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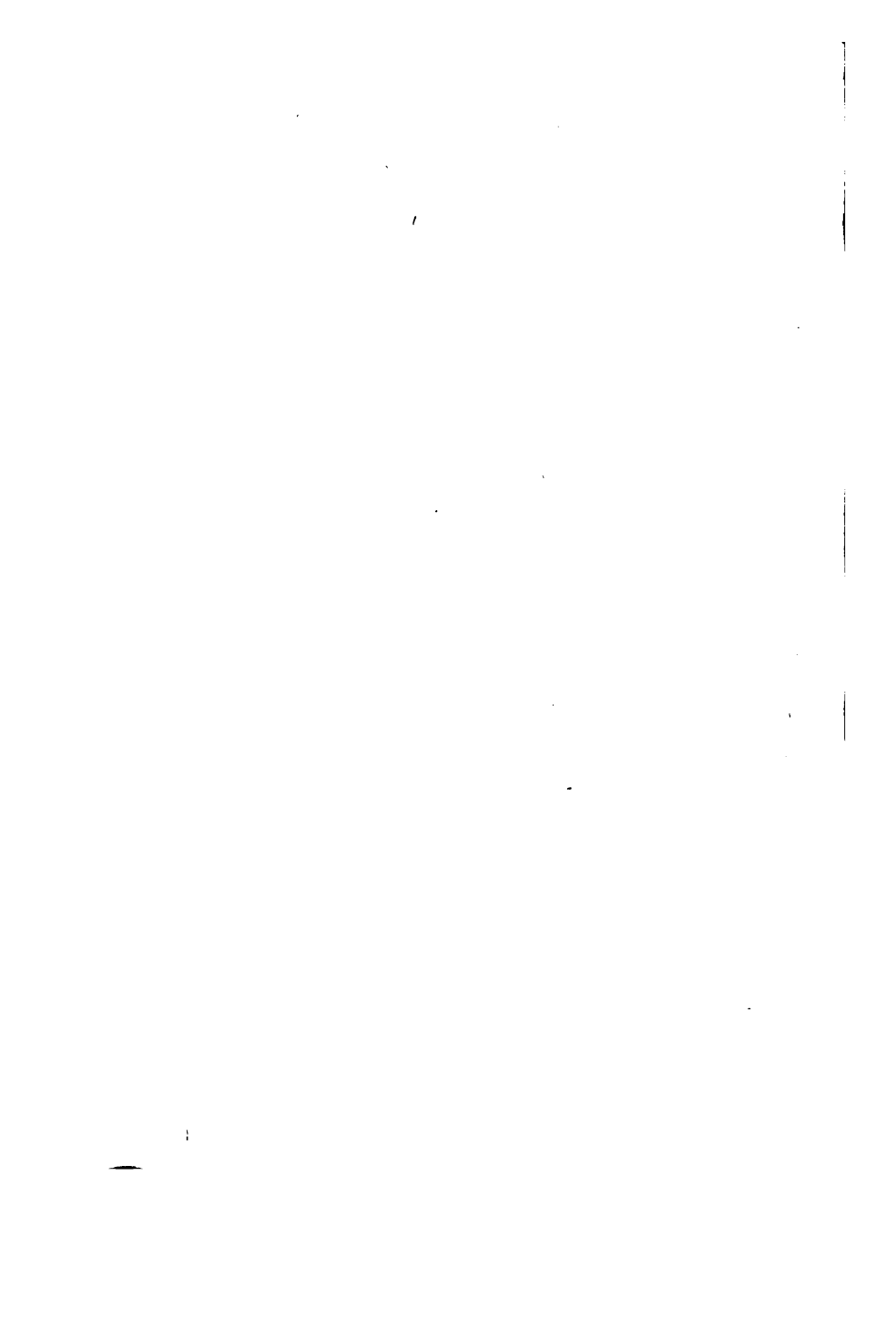
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The
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COMPRISING EIGHT VOLUMES ON THE
YEAR'S PROGRESS IN MEDICINE AND SURGERY

Under the General Editorial Charge of
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Volume VII

Skin and Venereal Diseases

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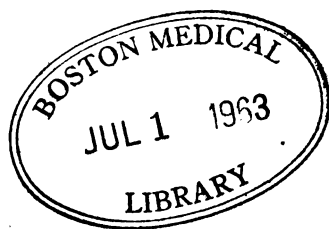


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SKIN AND VENEREAL DISEASES

DERMATOSES.

PROGRESS IN DERMATOLOGY.

Protein Sensitization in Production of Skin Disease. After a critical review of the literature, Towle¹ says that protein sensitization is now an accepted fact. The theories as to its meaning and its mechanism differ and much that has been published concerning the process lacks confirmation. There is still much work to do in allied fields, such as the diatheses and the intoxications, before full use can be made of the new cult. In the meantime, while accepting the principles of the cutaneous food tests, interpretation must await fuller, better defined understanding of the process of protein sensitization before it can attain its greatest efficiency.

Protein Sensitization in Skin Diseases. A critical discussion of the various theories, a review of the literature and the results of the tests applied in a series of cases appear in an article by Highman and Michael.²

Of the sixty-three positive reactions, thirty-seven were to vegetable and twenty-six to animal proteins. Reactions to more than one protein occurred in eleven of the twelve cases tested. Reactions to both vegetable and animal proteins occurred in ten cases. In one case only buckwheat was tried. Suprarenal extract was of benefit in eight cases; it was not employed in five and caused collapse in one.

The authors believe that urticaria and allied conditions, notably angioneurotic edema, are anaphylactic manifestations. Moreover, they believe the positive protein tests prove them to be anaphylactic. They believe that the protein food tests are of great value inasmuch as the tests indicate sensitization to a definite protein which, in treatment, is to be removed from the diet. One by one the various proteins should be given to the pa-

(1) Archiv. Dermat. and Syph., November, 1920.

(2) Ibid.

tient. Those provoking recurrences should be permanently eliminated. Desensitization is to be practiced only with important foods and particularly in infants and children in whom the diet is necessarily restricted. No cures can be expected unless the abnormal digestive tract, which is the avenue of sensitization, is treated.

Skin Reactions to Apthesine and Quinine. Idiosyncrasy of certain persons to drugs causing various skin rashes is of common occurrence, but the proof that an eruption is due to the ingestion of a drug is generally lacking. Mook³ has applied the well-known cutaneous tests in two cases, one of which was susceptible to apthesine, a local anesthetic, and the other to quinine, taken internally. The first patient was a dentist who had a subacute dermatitis of the index, second and third fingers of his left hand. The eruption on the index and second fingers chiefly involved the palmar surface of the last two joints, with a mild inflammation around the entire nail. The lesion was reddened, slightly scaly, crusted, with some oozing of serum, and showed a few small fissures. The eruption had been present five weeks. The patient was immediately informed that his eczema was due to some chemical that he was using in his work. Inquiry developed the fact that he was using apthesine as a local anesthetic. His method of procedure was to place a tablet in the barrel of a syringe, add water and then hasten solution by knocking the syringe on his third finger. The few drops lost on the fingers in this process were responsible for the eczema. He stopped work entirely and within one month the eczema was entirely well under local soothing preparations.

Mook prepared a 1 per cent. solution of apthesine and applied it to a small scarification on his right forearm with water controls, such as are applied in food sensitization tests. Within twelve hours a distinct wheal was produced at the site, $\frac{1}{2}$ inch in diameter, and at the end of forty-eight hours the locally produced dermatitis reached its maximum. It consisted of a localized area of redness with edema, 4 cm. in diameter. As novocaine is said to be a drug similar to apthesine, the experiment was repeated after recovery from the apthesine, with a

(3) *Archiv. Dermat. and Syph.*, June, 1920.

similar clinical result, but not quite so marked a reaction.

A medical student who stated that he was susceptible to quinine was tested by Mook in a similar way. At the site of inoculation there was very marked reaction which lasted for more than twenty-four hours.

Another patient, a physician who always developed an erythema after an injection of arsphenamine, was tested by applying the solution to a small scarification on his forearm with negative results.

[We have seen a large number of cases of acute and chronic dermatitis in dentists produced by novacaine, and two cases which were produced by apothesine.—M.]

Acidosis in Skin Diseases. Last year attention was called to the work of Barber⁴ on the etiology and treatment of seborrheic eruptions by the use of alkaline solutions. Barber's idea is that in all seborrheic eruptions there is an acidosis which leads, either directly or indirectly, to seborrheic eruptions. This year Sweitzer and Michelson⁵ give a review of their work, which was an attempt to confirm the results obtained by Barber. The clinical and chemical examinations of Barber and Semon led them to conclude that they had established two fundamental facts: (1) That the majority of patients with seborrheic manifestations show a remarkably increased alkali tolerance, many of them to an astounding degree; (2) that in nearly all cases active inflammatory processes cease and the eruption rapidly clears when the urine has been rendered alkaline. Barber and Semon did not examine the blood of their patients to determine whether there was a lowering of the alkali reserve because their investigation has been limited to chemical examinations of the urine.

In 1919, Schwartz, Levin and Mahnken reported the results of examinations of the blood to determine the alkali reserve in 139 cases of various skin diseases. They found that in 59.7 per cent. they were of normal value; in 35.9 per cent. there was a mild acidosis, while in 3.5 per cent. there was only a moderate acidosis. One patient had a severe acidosis, but the skin condition here was a

(4) Practical Medicine Series, 1919, Vol. VII, p. 8.

(5) Archiv. Dermat. and Syph., July, 1920.

complication of diabetes. In conversation, Rowntree, whose experience in acidosis studies is extensive, stated to Sweitzer that he had not encountered any particular skin manifestations in his work with patients suffering with acidosis, and the authors of this article conclude, therefore, that if the seborrheic state were a manifestation of acidosis it should be encountered with relative frequency by one who sees acidosis constantly, and in a large number of cases occurring in a variety of conditions.

In a series of cases Sweitzer and Michelson determined the alkali reserve and in cases in which there was a marked variation, or because of special indications, they did a complete metabolic study, including basal metabolism and thorough physical examination by an internist. This was done to rule out some other condition which might account for the acidosis present.

Barber and Semon point out that the exudative diathesis of infancy is often the forerunner of what they call a seborrheic diathesis in adult life. In the urine and blood chemistry studies of exudative cases they have not found any degree of acidosis; in fact, the reverse is the tendency. There is an increase in fluids and there is no acetone in the urine.

Sweitzer and Michelson were not able to find any literature on blood chemistry findings on patients with exudative diathesis. Inquiry among pediatricians disclosed the fact that in a large series of cases of acidosis observed, due to a variety of causes, no cases of infantile eczema or seborrheic dermatitis were encountered. In the studies of these authors they were unable to establish the existence of a seborrheic state or seborrheic diathesis. They have found no consistent change in the alkali reserve, and have not found even a mild acidosis which could not be accounted for. The alkaline therapy in their hands has not been successful. They have obtained better results by placing the patient on a fat-free diet and using the ordinary well-known lotions and ointments.

Universal Exfoliative Dermatitis from Sodium Cacodylate. A case of universal exfoliative dermatitis due to sodium cacodylate and resembling the exfoliative dermatitis which occurs after the use of arspenamine

is reported by W. A. Pusey.⁶ The patient was a man, 51 years of age, who had had psoriasis for four years. The condition had yielded from time to time to radiotherapy and to other agents. Finally he went to a sanitarium, where he was given a series of twelve daily injections of sodium cacodylate, each $\frac{3}{4}$ grain. A few days after the last injection, a redness of the skin appeared, which quickly became universal. In Pusey's opinion, the case should serve as a warning, for there are occasional cases in which the skin is markedly hypersensitive to arsenic. He has seen one case of arsenical palms which followed injections of a very small dose of arsenous trioxide (about 1/100 grain) given as a tonic for a week. Such cases indicate a danger which the use of arsenic entails, and with which the profession apparently is not generally familiar. They constitute another reason why arsenic should not be given indiscriminately, as it so often is, in skin diseases.

[Very serious consequences follow the long-continued ingestion of arsenic. In order to obviate this, every prescription should be marked "not to be refilled," because many patients, finding that their psoriasis or dermatitis herpetiformis is benefited by arsenic, continue to take it over long periods and eventually develop the pigmentation and hyperkeratoses, which may eventuate in epitheliomas.—M.]

The Etiology of Eczema. Hazen⁷ summarizes his views concerning the etiology of eczema as follows:

Eczema, while giving a definite clinical picture, is in reality due to the following causes: external irritation, external infection, local predisposition of the tissues, disturbances of the vegetative nervous system, disturbed food assimilation and urticaria. The latter is probably due to a protein hypersusceptibility.

The day will come when the word "eczema" will no longer be used, just as the word "rheumatism" is now passing from usage. There is no more relationship between a dermatitis due to external irritation and due to vagotonia than there is between a gonorrheal arthritis and a syphilitic one.

(6) *Archiv. Dermat. and Syph.*, January, 1920.

(7) *Ibid.*, June, 1920.

As clinical entities now well established, the following may be suggested: dermatitis due to external irritation; vagotonic dermatitis; urticarial dermatitis and dermatitis due to disturbed food assimilation (the eczema of young children). None of these conditions should be classified as eczema, as this only results in confusion and a failure to discover the cause.

Protein Sensitization in Eczema. A series of seventy-eight cases of eczema tested with protein by Ramirez⁸ gave positive skin tests in thirty. Like asthma, anaphylactic eczema occurs more frequently under the age of thirty years. Eczema associated with asthma or hay fever is usually anaphylactic. Only a small percentage of all eczema cases are anaphylactic, but it is essential that patients be thoroughly tested in order that they may be properly classified and treated.

The treatment of these patients consisted solely in the removal of the protein, giving a positive reaction from the diet. The skin scarification method was used and the reactions were called positive only when a definite wheal measuring 0.5 cm. in diameter appeared. In the cured and improved patients, the improvement was noticed within the first week. In the apparently cured individuals there had been no recurrence within six months, and in some cases one year, although they were taking small quantities daily of the food to which they were originally sensitive. Skin tests performed six months later in six of the cured patients gave negative results.

A Fatal Case of Recurrent Scarlatiniform Erythema. A fatal case of recurrent desquamative scarlatiniform erythema in which three attacks occurred during a period of several months and ending in death, without autopsy, is reported by Grindon.⁹ Each attack was accompanied by high fever. There was also tenderness over the gall-bladder region and, preceding death, an attack of severe jaundice. The recurrent scarlatiniform erythema was probably a cutaneous manifestation of hepatic disease.

Acnitis of the Face. An extensive case of acnitis in which animal inoculations of the tissue were negative for

(8) *Archiv. Dermat. and Syph.*, September, 1920.

(9) *Ibid.*, November, 1920.

tuberculous lesions and tubercle bacilli is reported from the clinic of Jeanselme by Burnier and Bloch.¹

Etiology of Alopecia Areata. After twenty years of study of alopecia areata, Sabouraud² puts down some of his observations concerning the disorder and his conclusions concerning the etiology. After a consideration of all the various doctrines, he comes to the conclusion that there is not a single one that can withstand the investigation of our present-day knowledge. Alopecia areata appears as the syndrome in a number of conditions. It may be observed as a hereditary manifestation in some families. It occurs in connection with vitiligo or with exophthalmic goiter. It also occurs in women as a manifestation of a precocious or late menopause; or in the adult in connection with late eruption of the wisdom teeth. In a very few cases it has some connection with acquired or hereditary syphilis, especially in syphilis of the late type. This can be proved by the marked improvement which results from antisiphilitic treatment.

The Effect of Light on Vitiligo. In the Practical Medicine Series, 1918, Vol. VII, p. 9, the work of Bloch on the pigmentation of the skin; on the pathogenesis of vitiligo, and the effect of rays upon the skin, was reviewed.

Aided by this work of Bloch's, Carl With³ carried out some interesting experiments with the light bath in cases of vitiligo. In giving a great number of light treatments for vitiligo, he found that the lesions become visible whereas before the treatment with the light they were difficult to perceive. On the other hand, he was not able to produce new lesions of vitiligo. It was found that the carbon arc light produces on the vitiligo patches a macular pigmentation more or less pronounced. This spreads from the periphery to the center and may last at least fourteen months. In three cases the pigmentary process continued after the light bath had ceased. It is true that the vitiligo patches reacted with a stronger erythema than the pigmented skin did, but little by little the patients were able to withstand the quantity of light

(1) Bull. de soc. franc. dermat. et de syph., June, 1920.

(2) Ann. de dermat. et de syph., April, 1920.

(3) Brit. Jour. Dermat. and Syph., May, 1920.

to which they formerly reacted with an erythema, not only upon the pigmented but also upon the vitiliginous regions of the skin. Consequently, the skin had strengthened itself against the light in a way other than by pigmentation. The final proof that the rôle of the pigmentation is to form a protection against light has not yet been brought forth. So many observations, however, go to show that it must do so that this was the probable conclusion.

Arsenic Poison as a Possible Cause of Scleroderma. In three consecutive cases of diffuse scleroderma studied by Ayres⁴ at the Massachusetts General Hospital within the past six months, the urine has given positive tests for arsenic. One patient, a storekeeper, had kept powdered arsenate of lead under the counter for over four years to kill mice; another had handled glazed paper in a paper box factory for ten years; the third had been exposed to the use of insecticides about the house for a number of years but, so far as could be ascertained, this occurred after the onset of the scleroderma. Further investigation into the records of two other patients, who had died, showed that they had probably been exposed to arsenic. All five of these cases were examples of diffuse scleroderma with brown pigmentation. The condition of the three patients seen by the author and whose urine was positive for arsenic began with sclerodactylia.

Scleroderma and chronic arsenic poisoning possess many symptoms in common in individual cases, such as neuritic manifestations, pigmentation, cutaneous alterations of various kinds, loss of weight with muscular weakness, intermittent, irregular fever, gastro-intestinal disturbances, vasomotor instability, rapid and irregular heart, and menstrual disturbances. Therefore all cases of scleroderma should be carefully investigated concerning the possibility of arsenic poisoning.

Necropsy Findings in Congenital Scleroderma. The differentiation of edema neonatorum, sclerema neonatorum and scleroderma has been carefully and exhaustively discussed by Lieberthal.⁵

Weidmann⁶ has had the opportunity of making an

(4) *Archiv. Dermat. and Syph.*, December, 1920.

(5) *Practical Medicine Series*, 1918, Vol. VII, p. 77.

(6) *Archiv. Dermat. and Syph.*, April, 1920.

autopsy on a fifteen-day-old baby, probably syphilitic, which died of enteritis and meningitis. The lesions in the skin suggested sclerema neonatorum, but the lesions were symmetrical and peri-articular, and at necropsy the induration was found to be purely subcutaneous. On these and other grounds a diagnosis of sclerema neonatorum was rejected and the case finally placed in the general group of scleroderma without affixing any new name to the purely subcutaneous form. The author believes it to be of the same known nervous causation as many other cases of scleroderma.

The case may some day be valuable in that this symmetrical, peri-articular form of scleroderma may prove to afford a useful differential clinical diagnostic feature by pointing to a co-existent meningitis; and if another of these rare cases should come under observation, efforts should be made to obtain a sample of the spinal fluid by lumbar puncture which in this case was not done during life.

Congenital Ectodermal Defect. A very rare case of congenital ectodermal defect characterized by a congenital absence of teeth, alopecia totalis and absence of sweat and sebaceous glands is reported by Goechermann⁷ (Plate I). The case is the second in the American literature and the sixth reported in the world's literature. It is unique, however, in the fact that the developmental defects occurred in a female, inasmuch as all the other cases reported occurred in the male. All the patients in this group present a facies very closely resembling that of congenital syphilis. The influence of syphilis in the production of these congenital defects, however, is probably *nil*. The reported cases of this group of ectodermal defects have exhibited a total absence of sweat glands and almost total absence of sebaceous glands, a hypotrichosis with absence of lanugo hair, and dental aplasia. Such patients suffer from a disturbance of the heat-regulating mechanism, depending on the inability of the skin to eliminate the necessary amount of water to keep the temperature level under varying external conditions. Valuable contributions to the conceptions of certain phases of the physiology of the skin have been made by

(7) *Archiv. Dermat. and Syph.*, April, 1920.

experiments on patients with this type of congenital defect.

Folliculitis Decalvans and Lichen Spinulosus. Attention was first called to this combination when Graham Little presented a case before the Dermatological Section of the Royal Society of Medicine in 1915. In the same year and before the same society, Dore presented another case and in the same year Beatty of Dublin presented still another case. In November, 1919, Ormsby of Chicago demonstrated a case of this type before the Chicago Dermatological Society.

Senear⁸ describes a case presenting folliculitis decalvans in the scalp and lichen spinulosus of the body. The patient was a woman, 30 years of age, who had had the disorder since she was 9 years old. At that time her hair began to fall rather rapidly and the alopecia became permanent. This alopecia has slowly progressed since that time. About eight years before coming under observation, she developed an eruption over the back which she stated was similar to the attack which was present at the time when she was seen, but it cleared up spontaneously. The first lesions appeared over the nape of the neck, followed by others over the occipital region, shoulders and back. The hair had been shed rapidly again after this eruption appeared on the body. The patient's personal history disclosed nothing of interest. When examined the patient had an extensive alopecia with marked atrophic scarring of the type seen in folliculitis decalvans. The process which had produced this atrophy was still active, and there were numerous follicular papules and a few pustules present. The other eruption, involving the nape of the neck, lower occipital region, shoulders, back and upper arms, consisted of variously sized groups of follicular lesions. The individual lesions varied from reddish follicular papules, slightly elevated, to definitely elevated and spinous lesions, some of them having rather long slender spines. In the largest patches, the lesions had slightly inflammatory areolae, so that the group picture showed an erythematous background with elevated follicular lesions.

Four of the five cases now on record occurred in

(8) *Archiv. Dermat. and Syph.*, August, 1920.

women. Ormsby's patient was a man. In all, folliculitis decalvans was of long standing followed by the rather sudden development of a follicular eruption on the body, the clinical picture of which was like that of lichen spinulosus. In all cases the condition on the scalp was obviously folliculitis decalvans, but the body eruption was more puzzling.

No one as yet has satisfactorily explained the co-existence of two disorders of such obscure etiology. It is difficult to consider the eruption on the body as folliculitis decalvans, since in none of the four cases was there any atrophic scarring in the body lesions, as is the case when folliculitis decalvans affects parts other than the scalp. Furthermore, the body eruption was too acute. Senear, however, offers one hypothesis which is founded on a comparative basis.

We are familiar with other follicular eruptions, which are looked on as the manifestations of the activity of toxins secreted by infectious organisms affecting distant parts of the body. The most familiar example of this kind is the lichen scrofulosorum type of tuberculide. More recently we have become acquainted with the group of trichophytide, first described by Jadassohn in 1911, consisting for the most part of lichenoid eruptions occurring on the body in children affected with trichophytosis capitis, usually kerion celsi. In a number of these cases, the eruption assumed a type clinically indistinguishable from lichen spinulosus, as shown by Jadassohn, Bloch, Guth, Rasch and others. There are, therefore, some points in common with the above conception of the etiology of lichen scrofulosorum and lichenoid trichophytides; folliculitis decalvans is probably due to a chronic infective process, which, theoretically at least, might be able to elaborate toxins responsible for the production of lichen spinulosus.

HERPES ZOSTER.

Herpes Zoster and Varicella. The number of cases of associated herpes zoster and varicella reported in the literature was placed by LeFeuvre in January, 1915, at

forty. Four years later, Low states that over fifty have been recorded. McEwen⁹ reports a case and reviews the literature. He finds that probably somewhat less than fifty cases have so far been reported, but inasmuch as a number of references were not available, the correct number is probably in the neighborhood of sixty. For the purposes of review, the cases reported are grouped into four classes:

Group 1. *Herpes zoster in one patient followed by varicella in others who were exposed:* Fully two-thirds of all the reported zoster-varicella cases belong to this group. In cases of this group the patient has an attack of zoster and about fourteen days later varicella is found in some one exposed to the zoster patient without discoverable exposure to varicella elsewhere. In explanation of these cases Bokay, who reported nine instances of the association, advances the theory that under certain unknown conditions the infective agent of varicella produces a local zosteriform eruption instead of a generalized exanthem; the zoster is thus an expression of varicella, and contagion is readily passed to others.

Group 2. *Herpes zoster in one patient; followed by varicella in the same patient; not followed by varicella in others who were exposed:* The author finds the description of the cases reported falling in this group are either so meager or so faulty as seriously to bring into question the correctness of the diagnosis. Either the case was generalized herpes zoster or varicella zoster or varicella in the one case. In this group the term "aberrant vesicles" and "generalized zoster" cause considerable confusion. These eruptions may closely simulate varicella, and it is especially interesting that the rash in the generalized cases is practically always described in terms which link it with the idea of varicella. A varicella erroneously called a "generalized zoster" remains a varicella and *vice versa*.

Group 3. *Herpes zoster in one patient; followed by varicella in the same patient; followed by varicella in others who were exposed:* The cases fitting the requirements of Group 3 seem to be of extreme rarity. The case reported by the author is in this group. In the litera-

(9) Archiv. Dermat. and Syph., August, 1920.

PLATE I.



Congenital ectodermal defect, showing the characteristic nose which resembles the "saddle nose" of congenital syphilis. The scalp is covered by a wig which hides the almost total alopecia. —Goeckermann, page 13.



ture, the author was able to find only two previously reported cases which might, by liberal interpretation, be placed in this group. Neither of them, however, was a clear-cut case.

Group 4. *Varicella in one patient; followed by herpes zoster in others who were exposed:* Cases which appear in this group are lacking in clinical detail and prove little or nothing; they are, however, extremely suggestive of important possibilities.

The author advises, in order to clear up the confusion which has resulted from the term "generalized herpes zoster," that the term should be abandoned as indefinite and inaccurate and a new nomenclature established. This group should be arranged under the captions as follows: (a) Herpes zoster with aberrant vesicles in the neighborhood of the zoster area; (b) herpes zoster attended with a general eruption, and (c) multiple herpes zoster, to include bilateral and universal cases.

Co-existing Facial and Thoracic Herpes Zoster. A survey of the literature on the subject leads H. W. Barber¹⁰ to believe that his case of herpes zoster involving simultaneously the ophthalmic division of the fifth nerve and the thoracic nerve is unique. Typical lesions were present on the left chest along the seventh dorsal segment and on the left forehead, left temple and the left of the bridge of the nose. The conjunctiva of the left eye was reddened and injected, but no actual vesicles were seen either on the conjunctiva or cornea. The conjunctiva of the right eye was normal in appearance. The glands of the pre-auricular and axillary group were markedly enlarged. The case healed uneventfully.

SKIN LESIONS IN THE LEUKEMIAS.

Lymphogranulomatosis of the Skin in Hodgkin's Disease. The patient whose history forms the basis of a report by Howard Fox¹ was an ex-soldier of the regular army, 30 years old, who presented a moderate, painless enlargement of various groups of lymphatic glands,

(10) Lancet, Dec. 20, 1919.

(1) Archiv. Dermat. and Syph., November, 1920.

enlargement of the spleen and liver, a normal blood picture, except for a mild anemia, dyspnea on exertion and increasing asthenia. At the time of writing, his illness had existed fifteen months. A histologic examination of an excised gland showed a typical picture of a lymphogranuloma, including the presence of uninuclear and multinuclear giant cells of the Dorothy Reed type.

The cutaneous lesions consisted of tumor-like infiltrations of portions of the scalp, forehead and midscapular region. Histologic examination of tumor from the scalp showed a similar structure to that of the gland. No increase of eosinophils was present in either gland or cutaneous tumor. Thorough examination (physical, Roentgen-ray and pathologic) failed to show any evidence of tuberculosis.

If the pathologic conception of Hodgkin's disease is limited to what Warthin speaks of as the "endothelial type," meaning the conditions described by Reed, Longcope and others, this case must be regarded as one of Hodgkin's diseases. As the cutaneous lesions showed a similar structure to that found in lymphatic glands, it should be classed as one of true Hodgkin's disease of the skin. This condition has been previously reported in only a small number of cases. This case may be added to those that tend to disprove the contention that Hodgkin's disease is related to tuberculosis. Mycosis fungoides can generally be differentiated clinically from Hodgkin's disease, though at times this may be difficult or impossible. The differential diagnosis, from the histologic standpoint, may also be difficult at a given moment. Until the causes of these diseases are definitely ascertained, it can not be settled with certainty whether or not mycosis fungoides should be considered as a cutaneous manifestation of Hodgkin's disease.

Lymphatic Leukemia with Primary Manifestations in the Skin. In lymphatic leukemia occasionally there are found lymphadenotic infiltrations in the skin and subcutaneous tissues that are a part of the general disease. These infiltrations consist of a hyperplastic lymphocytic elements and are generally supposed to be marrow lymphocytes transported by the blood-stream and deposited in the skin and subcutaneous tissues. These lymph-

adenotic changes occurring in or preceding lymphatic leukemia are of two forms: the circumscribed, or tumor, and the diffuse, or universal. The first is a nodular or tumor form, or a circumscribed leukemic, or aleukemic lymphadenosis of the skin. The second is a diffuse or universal leukemic, or aleukemic lymphadenosis of the skin.

A case of lymphatic leukemia following lymphadenotic skin changes of the circumscribed or tumor type is reported by Butler.² There are many interesting features in connection with this case which are described in detail. The disease began apparently with a throat infection. The first evidence of the disease was the development of the skin tumors. The blood picture was normal at the beginning and there were no blood changes until all the skin tumors were formed. Glandular and visceral involvement was not apparent in this case at any time. The skin tumors were made up of collections of large lymphocytes. When all the tumors were formed the blood showed a leukemia for the first time. The lymphocytic deposits showed numerous mitoses. The benzol treatment caused a partial regression and paling of the tumors.

Pruritic Decalvant Lymphadenique. Interest has again been aroused in prurigo lymphadenique of Dubreuilh and its connections with the leukemides and the lymphodermas not only because of the interesting lesions which occur in the blood-forming organs and in the blood itself but also because of the interesting and diverse cutaneous changes which occur in the course of these disorders.

Nanta and Baudru³ report an interesting case which has some unusual features and give an exposition of the present-day views concerning the various leukemias and of Hodgkin's disease and of the cutaneous changes which take place.

At present, the four following types are recognized:

1. A type of typical hyperplasia, either diffuse or localized, which is called lymphadenemia and of which there are two types: The one is a hyperplasia of myeloid character and the other is a hyperplasia of lymphoid

(2) *Archiv. Dermat. and Syph.*, November, 1920.

(3) *Ann. de dermat. et de syph.*, March, 1920.

character, both of which may be accompanied by leukemia or may be aleukmic. No organism has been isolated which can be demonstrated as the cause of this disorder.

2. A type of hyperplasia which is of a diffuse, inflammatory character and of granulatous nature which was described by Paltauf-Sternberg and which is ordinarily known as Hodgkin's disease: This disorder is characterized by its malignancy, its eosinophilia, its various clinical complications and its marked resistance to radiotherapy. Moreover, various organisms have been isolated which have been claimed to be the causative agent.

3. A type of hyperplasia which is of an inflammatory character, which probably belongs to the tuberculosis of Sabrazès and Duclion: It is characterized by its histologic picture and the presence of the bacillus of tuberculosis and its reactions to tuberculin.

4. A typical hyperplasia which is probably a neoplasm: This is sometimes diffuse and sometimes regional; it may occur as a malignant lymphadenom or as a lymphosarcoma. It is characterized by extensive metastases.

The last three types of hyperplasia may give rise to a marked leukocytosis ranging from 20,000 to 40,000 white cells. One of these, Hodgkin's disease, is usually recognizable by not only the blood eosinophilia but by the tissue eosinophilia as well.

All four of these types may give rise to cutaneous reactions which are much the same in all cases but which vary greatly from one case to another. Audry has grouped all of the exanthems, the papulo-vesicular exanthems, the urticarias, and prurigo under the name of "*leucémides*."

The cutaneous reaction is composed of four main elements; namely, pruritus, eosiniphilia, prurigo, and lymphogranulomatosis.

The pruritus may occur in any type of the lymphadenia or even in any type of adenopathy. Schaumann reports the observation of a lymphatic leukemia in which there were 200,000 cells and in which the treatment with radiotherapy invariably provoked a severe attack of pruritus and prurigo which disappeared on

cessation of treatment. Blaschko reported observation of the removal of a tumor of the breast which resulted in the cessation of a very marked pruritus, and which recurred with the development of a neoplasm in the site of the former tumor. The pruritus is probably due to leukocytolysis as the result of the treatment with radiotherapy. The presence of eosinophilia is not necessary for the development of pruritus.

The prurigo is not always present and may be entirely independent of the pruritus. The pruritus may be intense and continue to the day of death, without ever having been associated with the development of the typical prurigo.

The case studied by Nanta and Baudru occurred in a woman 20 years old who had had a persistent and intractable pruritus for five years prior to coming under observation. For the past two years she had been losing her hair. There was no eruption on the body. At one time she had developed a substernal tumor, the size of an egg, which had been excised.

At the time of coming under observation the patient was markedly emaciated and the skin of the entire body was much thickened and had lost its elasticity. The hair of the head had practically disappeared, as well as the eyebrows, which were almost rubbed off. There was a generalized and marked adenopathy which was greatest in the axillary region and in the inguinal regions. The pruritus was generalized, intense and permanent, but there was no evidence of excoriation on the skin. The leukocytosis amounted to 22,000, of which 5 per cent. were eosinophiles. The tuberculin injection gave no local or general reaction. Radiotherapy gave a slight amelioration of the pruritus.

Histologic examination of the extirpated glands showed a marked sclerosis with a moderate amount of lymphocytic infiltration. The typical lymphogranulomatosis of Hodgkin's disease was entirely absent. Histologic examination of the skin showed no very marked alteration. In the epidermis there was augmentation of the pigment of the corneus layer and a relative atrophy of the statum granulosum with a moderate amount of pigmentation. In the derma there was a very slight change in the papillary bodies.

THE LICHENS.

Lichen Nitidus. Another case of lichen nitidus has been seen by Sutton,⁵ who described a case in 1910. The patient was a young man 27 years of age who had had the disorder for eighteen months. The most characteristic lesions were to be found scattered over the flexor surface of the forearms. In these localities, the elevated, pinkish or reddish, flesh-colored, oval or flat-topped papules were interspersed with areas of normal skin, and exhibited but little tendency to grouping or coalescence. A few were marked by minute, central depressions. At the wrist, the little lesions were more closely placed, six or eight, or even more, sometimes occupying a space no larger than the top of a lead pencil. Here the color also changed. Instead of being pinkish or yellowish in hue, the papules were reddish or violaceous, and on the lateral and dorsal surfaces of the wrist, this variation in color was even more striking. The surface of the lesion was invariably smooth and the skin comparatively soft, differing in this respect from the hyperkeratinization so characteristic of long-standing patches of lichen planus. Subjective symptoms were wanting. Over the abdomen and thighs, the lesions were more sparsely distributed, and in these localities they bore a considerable resemblance to those of lichen scrofulosus. The histologic picture was that usually seen in this disorder. There was no evidence of tuberculosis in the patient and he did not react to tuberculin injections.

Clinical Studies of Lichen Planus. A clinical study of the records of 179 cases of lichen planus and a tabulation of the various features of the disease is made by Jacob.⁶

Considerable attention is devoted to a discussion of the etiology of lichen planus. The author could find no evidence of severe nervous shock as being an etiologic factor. The characteristics of the cutaneous lesion and the course of the disease lead him to accept the theory of a toxic or microbic origin.

In the treatment of lichen planus, mercury, arsenic

(5) *Archiv. Dermat. and Syph.*, July, 1920.

(6) *Ibid.*, November, 1920.

and Roentgen rays were found to be efficient. In acute cases mercuric chloride, either intramuscularly or by mouth, in gradually increasing doses was of value. It was noted in many cases that the symptoms of nervousness, irritability and pruritus disappeared under mercury some time before the eruption was influenced. In the subacute cases, protiodide of mercury or Fowler's solution was used and in practically all of these, one or the other was found to effect a cure. In the chronic cases, arsenic in the form of Asiatic pill was the most efficient remedy. Some few localized hypertrophic cases of long standing which could not be cleared with any other remedies, responded to the Roentgen ray. It was found that arspenamine and its derivatives were of little or no value in the treatment.

Among more than 8,000 patients with various dermatoses, Culver⁷ found 148 cases of lichen planus. A clinical study of these cases leads Culver to conclude that the disease must be considered constitutional. No evidence was found of its infectivity. The result of study of prodromal symptoms was negative; also there was no possibility of predicting the duration of the disease. The predisposing causes were found to be: sedentary occupation, sedentary habits, excesses or faults otherwise in eating and drinking, nerve strain or any other depleting influence. The nervous element in the disease is not so much a causative factor, he thinks, as it is a coincidence, and a result of some toxemia which is an essential element of the disease entity. Treatment must be constitutional as well as local.

Lichen Planus Linearis Along a Cutaneous Nerve. Lichen planus occurring in narrow lines, although comparatively rare, has been recognized for a number of years. Ketron⁸ reports a case which he observed in a man 33 years old, who had an eruption of lichen planus linearis along the back of the hand which had been present fourteen or fifteen years. It had begun on the back of the right hand and reached the present dimensions gradually within four or five years. It had remained unchanged for the past ten years. The clinical diagnosis

(7) *Archiv. Dermat. and Syph.*, January, 1920.

(8) *Ibid.*, September, 1920.

of lichen planus linearis was substantiated by the histologic examination. The eruption followed the course of the inferior external branch of the musculospiral nerve to its cutaneous end, which is usually at the wrist. Beyond this point it lay on territory supplied by one of the branches of the radial nerve.

Because of the possibility of the disease being dependent on some disturbance in this branch of the musculospiral nerve, it was thought advisable to sever it and note the effect on the eruption. An incision was made through the skin at right angles to the affected line about the middle of its course. It was carried through the subcutaneous tissue beneath which a small nerve trunk about 2 mm. in diameter was found lying on the muscular fascia. This nerve lay directly beneath the eruption and at this point ran parallel to it. The nerve was severed and a small piece removed for histologic examination but, unfortunately, was lost.

The effect of severing the nerve was to produce an area of complete anesthesia to pin pricks which extended 11 cm. below the point of incision and ended just above the level of the lower end of the radius. This anesthetic area followed the course of the eruption and averaged about 3 cm. in width. All the lesions in this area lay within it. The patient was observed for two or three weeks and then lost sight of for seven months. An examination at the expiration of this time showed that there was no noticeable change in the appearance of the disease and that the area of anesthesia had completely disappeared except over the scar from the incision. He also reported that he had noticed no change in the disease during his absence except the loss of itching over the anesthetic area.

Lichen Planus Atrophicus Limited to the Face.

Lesions of lichen planus atrophicus are commonly seen on the neck and upper chest but it is quite rare to find them limited to the face. Such an observation was made by Hudelo and Bouteiller.⁹ The lesions varied in size from that of a lentil to that of a one-franc piece. They were situated on the brow, on the forehead, on the left ear and at the right angle of the jaw. The lesions had

(9) Bull. soc. franc. de dermat. et de syph., 1920, No. 7, p. 257.

been present for three years and the Wassermann reaction was negative. The diagnosis of flat cicatricial epithelioma was considered but was rejected because of the multiplicity of the lesions.

PSORIASIS.

Chrysarobin as a Cause of Psoriasis. In support of the contention that chrysarobin is the cause of psoriasis in some cases, E. Ward¹ reports a case of psoriasis that had been treated for years with a chrysarobin ointment containing 5 grains to the ounce. This ointment had, as a rule, removed the lesions. Wishing to accelerate this cure, he applied an ointment containing 10 grains to the ounce. Immediately after the application of this stronger ointment there was a fresh outbreak of psoriasis papules occurring in a circle at the inner margin of the red zone. A milder chrysarobin ointment removed the new papules successfully.

[It is a matter of common observation that any inflammatory process in a psoriatic may serve to localize the lesions; for instance, the application of a plaster, a scratch, a pin prick, rubbing of the clothing or an insect bite may serve to produce lesions of psoriasis at the point traumatized. It is frequently observed that each needle puncture resulting from autoserum therapy in psoriasis will produce a psoriatic papule. The production of a dermatitis by chrysarobin is no exception to this rule. Apparently about the lesions of psoriasis in this case a dermatitis resulted and in this area of dermatitis, new lesions appeared.—M]

The Lungs in Psoriasis. The connection between tuberculosis and psoriasis has long been the object of study. Audry has reported a case in which psoriasis and erythema induratum co-existed. Petges observed a case of chronic synovitis in a psoriatic. Milian obtained reactions analogous to those in tuberculosis in a psoriatic by the injection of tuberculin.

Lévy-Franckel and Jacob² made clinical and radio-

(1) Brit. Jour. Dermat. and Syph., October, 1920.

(2) Bull. soc. franc. de dermat. et de syph., 1919, p. 324.

scopic examination of the lungs in forty-nine cases of psoriasis. Of these, fifteen were found to be free from tuberculosis; twenty-seven showed definite lesions, and six showed very mild or doubtful lesions. The authors make no attempt to prove the tuberculous nature of psoriasis but from the figures offered, they are inclined to the belief that the tuberculous terrain is favorable to the development of psoriasis.

Menace in the Low Protein Diet in Psoriasis. Attention is called to the danger of a low protein diet by J. C. Michael³ of Houston, Texas, in patients who may present a prediabetic condition. Since the investigation of Schamberg and his collaborators on the protein metabolism in psoriasis, and the distinctly beneficial results obtained by them in this disease by restricting the nitrogenous intake, it has become more or less a routine to place the patient with psoriasis on a low protein diet. In reducing the protein intake the caloric requirements are made up usually by carbohydrates and fat. Practically, the increase occurs most often in the carbohydrate components, since they are more agreeable to the majority of patients. Such a diet, rich in starches and sugars and poor in proteins, is in some cases kept up for a long time, either by order of the physician or by the volition of the patient.

Diabetes is recognized universally as a contraindication to a diet rich in carbohydrates, but it is not so generally recognized that there exists a detectable prediabetic state in which a diet of this kind leads to permanent glycosuria. To continue a prediabetic patient on a diet rich in carbohydrates is likely to lead to the development of diabetes. Studies made of two such cases are reported in detail. The lowered glucose tolerance was demonstrated in both cases by percentage of blood sugar.

Keratoderma Blennorrhagica as a Form of Psoriasis. The association of psoriasis with rheumatoid arthritis has been observed from time to time and has been the subject of considerable literature. In some cases that have come under the observation of H. G. Adamson,⁴

(3) Archiv. Dermat. and Syph., October, 1920.

(4) Brit. Jour. Dermat. and Syph., June, 1920.

the patients have suffered from rheumatoid arthritis associated with more or less extensive psoriasis of the limbs or trunk, and with heaped-up, horny-looking lesions on the palms and soles, which have borne a close resemblance to the well-known horny-looking cones of gonorrheal hyperkeratosis. The author reports in detail three cases, all of which occurred in women in whom there was no history or any evidence of gonorrhea. The diagnosis in each case was arthropathic psoriasis, but the resemblance of the palmar or plantar eruption to keratoderma blennorrhagica was so close that it at once recalled that affection. The author finds, moreover, that there are many cases of gonorrheal hyperkeratosis in which there are eruptions on the limbs or trunks indistinguishable from psoriasis. There are other cases in which it is difficult or impossible to make a definite diagnosis between arthropathic psoriasis and gonorrheal hyperkeratosis. The histopathology of psoriasis and of keratoderma blennorrhagica resemble each other very much.

LUPUS ERYTHEMATOSUS.

Lupus Erythematosus and Streptococcus Infection.
In 1915 H. W. Barber demonstrated a case of lupus erythematosus before the Dermatological Section of the Royal Society of Medicine in which there was found in the feces *Streptococcus longus*. Recently, Barber⁵ has seen another case in which there was a focal infection of the tonsils, also with *Streptococcus longus*. The tonsils were the only discoverable focus of infection, and in the opinion of the author were responsible for the constant pyrexia when the patient was up and about. The tonsils were removed and a vaccine made from the culture of *Streptococcus longus*. With each injection of the autogenous vaccine there was not only a constitutional reaction but also a definite focal reaction in the patches of lupus erythematosus. Moreover, the persistent pyrexia, provoked by an overdose of vaccine, was accompanied not only by aggravation of the inflammation in the original patches, but by an actual spread

(5) Brit. Jour. Dermat. and Syph., October-December, 1919.

of the eruption as an acute erythema. At the time of the excision of the tonsils, some of the lymphoid tissue remained and subsequently an acute infection occurred in this lymphoid tissue. Simultaneously, there was a flare-up in the lesions of lupus erythematosus. The complete removal of all the infected lymphoid tissue and the institution of treatment with sensitized vaccine resulted in retrogression of all the lesions without any further active local applications.

Lupus Erythematosus and Focal Infection. A case of lupus erythematosus which had resisted all the well recognized forms of local applications, and which promptly improved after the extraction of the diseased teeth, is reported by M. D. Hartzell⁶ of the University of Pennsylvania. There was no bacteriologic examination made and the organism concerned is, therefore, unidentified. Along with this case Hartzell reports another in which no evidence of focal infection of any kind could be found.

A Fatal Case of Lupus Erythematosus, with Autopsy. The article of Barber⁷ on the association of streptococcus injection of the tonsil is of interest in connection with the case of lupus erythematosus studied carefully by Low, Logan and Rutherford.⁸

Clinically, the case was typical of generalized lupus erythematosus. The eruption was characteristic both in appearance and distribution. The illness consisted of four attacks during four and a half years with complete disappearance of symptoms in the intervals between the attacks. The second attack was not accompanied by fever and the eruption then was of the ordinary type of chronic lupus erythematosus, whereas in the other three attacks the eruption was more wide-spread and diffuse and accompanied by a continuously high temperature. The temperature never at any time resembled the swinging temperature associated with tuberculosis. During the third attack it seemed as if the patient were going to die, but the temperature suddenly fell and the individual made a rapid and complete recovery, only to succumb to the fourth attack.

(6) *Archiv. Dermat. and Syph.*, October, 1920.

(7) Page 27 this volume.

(8) *Brit. Jour. Dermat. and Syph.*, August-September, 1920.

It is difficult to draw conclusions from the results of the postmortem examination. It is not proposed to raise the whole question as to whether lupus erythematosus is a tuberculous manifestation or not. This patient undoubtedly suffered from fairly extensive chronic tuberculous lesions, but not any more extensive than are frequently seen in patients dying of other affections.

The most interesting feature in the case was the finding of a streptococcus in the heart-blood. Unfortunately, the case was complicated by the terminal diphtheria of the larynx. The question as to whether the streptococcus had been introduced into the blood shortly before death as a result of the diphtheria or whether it was there previous to that can not be decided. The fact that the blood culture made a month before death was negative can not be held as conclusive that no organisms were present at that time. One might be inclined to consider it a terminal infection because the organism gave the reactions which would place it in the *Streptococcus salivarius* group. This form of streptococcus is commonly found in the mouth and throat as a non-pathogenic saprophyte, but the fact that it grew in long chains is in favor of its pathogenicity. Apparently it is the same organism which was recovered by Barber from the feces and tonsils in his cases of lupus erythematosus. The only lesions which might have been due to the streptococcus were the pericarditis, and, possibly, the pleurisy. The pericarditis was subacute and evidently non-tuberculous. Is it not possible that the pericardial lesion was a focus from which a streptococcus septicemia might arise, because these cases of generalized lupus erythematosus, apart from the skin-eruption, have many features in common with cases of malignant endocarditis?

Low and Rutherford⁹ report another case of lupus erythematosus which came to autopsy and was carefully studied bacteriologically. At the time of admission the patient had bronchitis, with some edema of the ankles. He also had abundant purulent sputum which contained numerous staphylococci, Friedländer's bacilli and *Streptococcus longus*. The patient's teeth were bad and both upper and lower gums showed marked pyorrhea. All

(9) Brit. Jour. Dermat. and Syph., November, 1920.

bad teeth were extracted and a vaccine was made, three doses being administered at intervals of one week. As a result of the vaccine injections and the extraction of the teeth, the lupus erythematosus improved markedly. All the lesions became distinctly paler and less scaly and in places complete healing took place. Locally, the only treatment used was the application of boracic and calomine lotion.

The postmortem examination was conducted with special care to detect any tuberculous or streptococcus foci. In spite of a very thorough search, through all the glands, no trace of tuberculosis could be found either to the naked eye or microscopically. All doubtful glands were sectioned but with negative results. As the post-mortem examination did not take place until twenty-four hours after death, no attempt was made to cultivate any organisms from the internal organs. Unfortunately permission to examine the head could not be obtained but there was no symptom pointing to any lesion there.

The case is interesting from the fact that the eruption improved markedly after the extraction of the bad teeth and the administration of a vaccine containing *Streptococcus longus*. The complete absence of any trace of tuberculosis seemed to exclude that disease as the cause of the lupus erythematosus in this case. The presence of *Streptococcus longus* in the mouth and bronchi is suggestive that these areas might have been the foci of absorption. The improvement both in the lupus erythematosus and in the bronchitis after the removal of the teeth and treatment with the streptococcus vaccine supports this view.

Lupus Erythematosus of the Plantar Surfaces. Lupus erythematosus of the plantar surfaces is an extreme rarity and it is for this reason that a case seen in the service of Darier at Hospital Saint-Louis is reported by Perin.¹

The patient was a woman of 25 who had typical lesions of lupus erythematosus on the face. There were also lesions on the nose and the dorsal surfaces of the hands. The plantar surfaces of both feet were involved, but the lesions on the right were the more extensive. The lesions

(1) Bull. soc. franc. de dermat. et de syph., 1919, p. 314.

were sharply demarcated and occupied the entire plantar surface on the right except that of the inner arch. They were fairly well limited to the hyperkeratotic surface of the foot but in places extended beyond the borders for a few millimeters. There was no evidence of punctate keratoses nor of porokeratoses. The lesions on the left foot were similar to those of the right except in that they were less extensive. The lesion on the face had been present for ten years, but those on the feet had existed for only six weeks.

Histologically, the picture was that of lupus erythematosus. There was a corneous atrophy, and in the papillary body there was a cellular infiltrate about the dilated vessels.

Osseous Formation in Lupus Erythematosus. Calcification of various healed pathologic processes is not an uncommon observation, but ossification is an extremely rare process. Trimble² reports a case of lupus erythematosus which had healed lesions on the cheek and on the right buttock. The lesion on the right buttock was about four inches in diameter and of board-like hardness. It was finally removed by surgical excision and examined histologically and chemically. The author was satisfied by histologic and chemical examination that it was a case of true bone formation.

In the discussion which followed the presentation of the paper, however, various members of the society were inclined to dissent with the view of the author. They considered it calcification rather than ossification.

FOX-FORDYCE DISEASE.

Pruritic Papulo-Dermatitis of the Axilla, the Pubes, and the Breast. In 1902 Fox and Fordyce described two cases of a rare papular disease affecting the axillary region. Later Fordyce reported the observation of other cases, and in 1911 Haase reported the observation of a case which was similar and which affected the axilla, pubes and breast. A case which is apparently exactly similar to those which are described in America has been

(2) Archiv. Dermat. and Syph., March, 1920.

observed by Burnier and Bloch.³ According to these authors this is the first case of this type which has been recorded in France.

The patient was a young woman, a Polish Jewess, 23 years old, who presented herself for consultation because of markedly pruritic areas in the axilla, and the pubes which had been present for one year, and which disturbed sleep.

The eruption consisted of a multitude of very small papules in the axillary regions, somewhat elevated, rounded or conical and sometimes surrounding a hair. The consistence was rather firm and the papules were somewhat translucent, giving the impression of a liquid. However, when they were punctured, no liquid was to be obtained. There was considerable increase in the pigmentation but no evidence of lichenification. The hairs of the axilla were very sparse. Histologically, there was a marked acanthosis around the sudoriparous orifices and a marked periglandular and perivascular cellular infiltration with a great abundance of mast cells and a marked dilatation of the sudoriparous glands.

Etiologically, the disorder is characterized by occurrence of hyperexcitability in nervous women of Semitic race. Clinically, the lesions are characterized by the occurrence of isolated micropapules and of pigmentation and the absence of lichenification. The lesions appear in the axillae and pubes and about the breast. Histologically, they are characterized by hypertrophy of the sudoriparous glands. The disorder, therefore, is to be distinguished sharply from the group of circumscribed *neurodermites* of Brocq, in which the sudoriparous glands are atrophied.

Chronic Papular Itching Eruption of Fordyce. The clinical and histologic study of another case of the chronic papular itching eruption of the axilla and pubes first described by Fordyce and Fox has been made by Withers.⁴ Three other cases of the same disorder are reported but were not carefully studied.

The patient was a girl of 13, who complained of an uncontrollable and intense itching about the axilla,

(3) Bull. soc. franc. de dermat. et de syph., 1920, No. 3, p. 86.

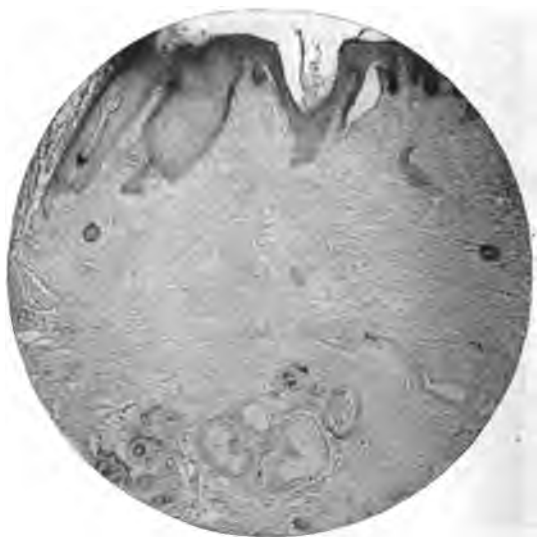
(4) Archiv. Dermat. and Syph., January, 1920.

PLATE II.



Chronic popular itching eruption of the axilla.—Withers, page 32.

PLATE III.

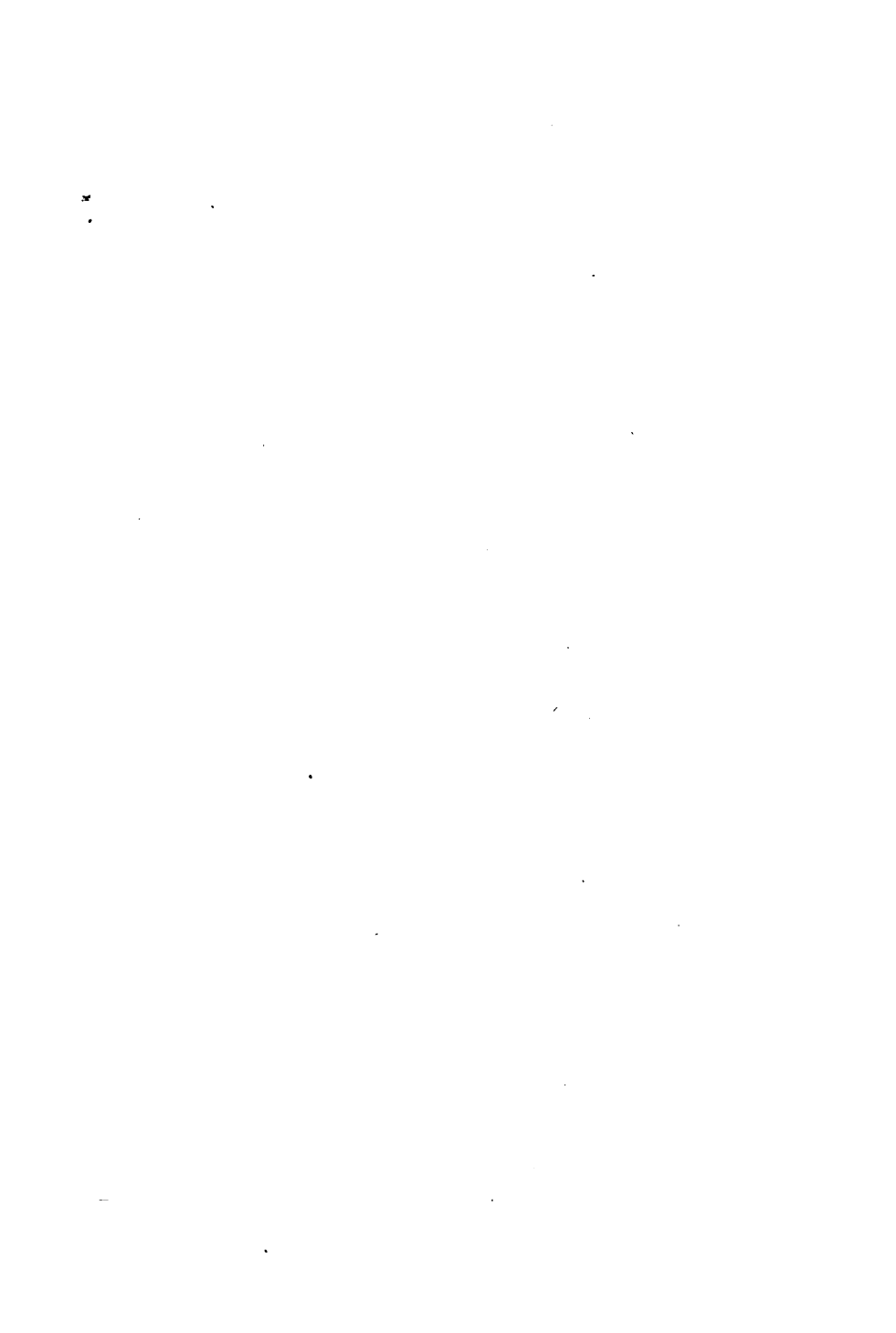


Photomicrograph of chronic papular itching eruption of axilla showing distention of the deep coils of the sweat gland.—Withers, page 32.

PLATE IV.



(Case 1.) *Psorospermiosis follicularis vegetans* (Darier's disease).—Wise and Parkhurst, page 36.



breast, perineum and pubis. The pruritus began at the age of 10 in the axilla which showed at that time no skin lesion other than that produced by scratching. Medications of various kinds were applied without avail. The condition became so irritating that the child had to be taken from school and restrained. The pruritus was aggravated during warm weather or by any exertion tending to cause perspiration, although there was no history of hyperidrosis or bromidrosis of the axillae at that time. The occurrence of itching and the inflammatory conditions set up by scratching were followed in two or three months by a thickening of the skin with brownish discoloration and small papules in both axillae. Within six or eight months after the initial lesion, there was noticed a similar uncontrollable itching about the vulva and the areolae of the breasts. Within the past year there has developed about the vulva and upon the abdominal wall above the pubis, a condition similar to that in the axillae.

The lesions consisted of hemispherical horny papules from one to three millimeters in diameter. These tended to occur in rows following the lines of cleavage in the skin which was thickened and thrown into folds. Some of the larger and older lesions contained black depressed plugs and were capped with hemorrhagic crusts. The more recent papules were glistening and showed a central depressed punctum. The central plugs were extracted with difficulty and caused bleeding.

Histologically, the changes consisted of acanthosis with hyperkeratosis, edema, perivascular infiltration and changes in the sweat glands with kerato-cystomata of the sweat glands. By far the most striking change was the enormous dilatation of the deep convolutions of the sweat glands and the hyalin degeneration of the lining. The condition was not amenable to local applications and grew steadily worse in spite of local and general medication. The patient was put on hygienic and dietetic routine tending to build her up constitutionally and decrease the nervousness. The condition has been improved only by such stabilizing treatment and as the nervous condition improved, the pruritis disappeared. The author agrees with Fordyce, Fox and Haase that this is a

chronic circumscribed dermatitis of neurogenic origin (Plates II and III).

Two cases of the Fox-Fordyce disease have been seen in Copenhagen by Rasch and Kissmeyer.⁵ The first patient was a woman 33 years old who had the disorder for ten years. The lesions were found in the axillae, in the pubic region around the genitalia and the nipple. This case was studied histologically but no mention is made of the dilatation of the glands as described by Fox and Fordyce.

The other patient was a woman 24 years old who had had the disorder for four years. The lesions were in the same region. Both cases manifested intense itching which disturbed sleep and made life almost unbearable. As in other cases described by Fox, Fordyce, Haase and others, the disorder resisted all forms of local applications. Radiotherapy was the only method of treatment of any value.

MISCELLANEOUS DERMATOSES.

Scorbutic Papulo-Keratotic Dermatitis. During the winter and spring of 1918, an epidemic of scorbutus developed in certain formations of the Roumanian army. At this time, Nicolau⁶ of Bucharest was struck by the fact that a large number of these patients suffering with scorbutus, presented a cutaneous eruption of decidedly special appearance characterized by keratotic, perifollicular papules. The author is not able to give exact figures concerning the frequency with which this eruption developed in scorbutus, but his impression is that it appeared in probably a fifth of the cases. He observed in all some forty cases which he studied intensively and a number of cases were carefully studied histologically. The essential lesion of this dermatosis is a minute cornified papule which is the result of an intrafollicular keratosis. About this primitive lesion developed more or less rapidly a process of infiltration of very slow development giving birth to papules of different

(5) *Dermat. Zeitschr.*, April, 1920.

(6) *Ann. de dermat. et de syph.*, 1919, p. 399.

dimensions and sometimes to papulo-pustules. The eruption begins in the large majority of the cases simultaneously on the antero-internal surfaces of the forearms and the antero-external surfaces of the thighs and also in the subumbilical region of the abdomen and on both sides of the white line. The eruption may remain in these regions for variable periods or even during the entire course of the disorder of the lighter cases. Generally, however, when it once appears it extends in a rather progressive fashion somewhat rapidly in the course of some weeks, and may become generalized. Once it is well developed it is remarkably symmetrical and is seen on the forearms, the upper arms, the shoulders, the thighs, the buttocks, the legs and, in the extreme cases, over the entire abdominal region, the flank and the larger part of the chest.

There are three types of cases: the very light, the medium and the extremely intense manifestations of this dermatosis. The disorder never becomes generalized; even in the most severe cases there are cutaneous regions, always the same, which are constantly respected. The regions which are always spared are the face, the scalp, the neck and the upper arm, the axillary spaces, the distal portions of the forearms, the hands and fingers, and on the lower extremities the inguinal region, the upper third of the leg, the feet and the toes. On the trunk the medio-thoracic region and the perineum and the region of the anus are spared. In the medio-thoracic region is a triangular area which is always spared and this is of diagnostic importance in differentiating it from the seborrheic dermatitis. On the back there is another large area between the scapulae and on the scapulae which invariably remains free from the disorder. The papules are rounded, of a convex surface which is in the form of a dome rather than acuminate and covered with a fine squama which is dry and which is like a covering of collodion. The papules are always dry without any tendency toward vesication and give to the touch a sensation of harshness. The general appearance of the disorder in this stage of development is that of keratosis pilaris of the white type. Lifting the white scale, one sees beneath it the follicle stoppered by a corneous mass.

The corneous growth is quite adherent and is very difficult to enucleate. In lifting it out with a pin, one is struck by the thickness of the plug and beneath it one finds an atrophic and rolled up rudiment of a hair. The large majority of the papules remain in the stage of follicular keratosis but a certain percentage of them undergo a transformation into perifollicular papules. Keratotic papules begin the transformation by becoming surrounded by an area of erythema which disappears completely under pressure. At first the erythema is purely macular but gradually it becomes papular. These perifollicular papules are rounded, firm to the touch, have a convex surface and are more or less elevated depending upon their dimensions. Generally they are covered with a fine scale and if one examines the papules closely it is possible to discover a central keratotic plug in the infiltrated mass. The color of the papules is a deep or violaceous red, particularly on the lower extremities where they sometimes acquire a purpuric cast. Some of the papules undergo very slight pustulation and when the pustule is opened, a small amount of pus can be expressed. The eruption is never pruriginous; in fact, is without any objective sensation. Once the scorbutic eruption is well developed, it may remain for months if the general conditions are not modified. On the other hand, under proper regime, the scorbutic eruption disappears rapidly, depending upon the improvement in the general condition of the patient. No local treatment in such cases is necessary. The difficulties of making a diagnosis of scorbutus early in the disorder are well known. Fortunately, this eruption may develop very early in the course of scorbutus and may be of some diagnostic value. So far as the author is aware this particular scorbutic eruption has not been hitherto described.

Darier's Disease. Two unusual cases of psorospermiosis follicularis vegetans have been reported by Wise and Parkhurst.⁷ The first case is further observation of a man whose case was first reported by Bulkley in 1890. The patient is now about 78 years old and has had the disorder for fifty-three years. The eruption was

(7) Archiv. Dermat. and Syph., October, 1920.

very extensive and the infiltrations into the skin were very pronounced, but the man complained more of discomfort and annoyance than actual itching and sensations of pain. He said that the eruption had changed very little in the preceding twenty years. At the time of this observation, however, a well-developed basal cell epithelioma was noted on the right side of the bridge of the nose. An interesting feature of this case is that in 1890 a statement was made by Bulkley that none of the patient's children presented any eruption. However, a daughter later developed the dermatosis and died at the age of 38 of endocarditis.

In contrast to the extensive and severe eruption in the first case, the second patient, a young woman, presented widely scattered, rather vaguely defined efflorescences which gave rise to no subjective sensations and constituted nothing more than a cosmetic defect. A clinical diagnosis was made with great difficulty and it was only after microscopic examination of the specimens that it was possible definitely to establish the diagnosis. Co-existent with the dermatosis were areas of macular atrophy on the chest, intermingling with numerous *læne atrophicae*. The co-existence of Darier's disease and atrophia maculosa cutis has not, so far as the authors are aware, been thus far recorded (Plate IV).

Discrete Urticaria Pigmentosa. The case of a child 7 months old with only three lesions of urticaria pigmentosa is recorded by Thibierge and Boutelier.⁸ Friction of these lesions led to typical urtication. There was no pruritus and no histologic examination.

Acrodermatite Suppurative Continue (Hallopeau). Without attempting to contribute anything to the subject, Bodin¹ reports in detail four cases which he has observed and studied. The first case occurred in a young woman 32 years of age in whom the eruption had an undoubted association with the menstrual function. In the second case, a man 45 years old, suffered constant traumatism from his work as a stone mason. In two other cases the eruption was localized on the fingers of

(8) Bull. soc. franc. de dermat. et de syph., 1920, p. 9.

(1) Ann. de dermat. et de syph., 1920, p. 193.

infants and in these cases the etiology and the origin were even more obscure than in the other two.

The author is unable to decide whether this disorder represents a dermatologic entity or simply a cutaneous reaction of a particular type having certain characteristics which would lead one to believe that they might be classed with other dermatoses.

In 1903, Bodin expressed the opinion that in some cases the disorder might be a localized manifestation of dermatitis herpetiformis. A number of cases of pustular dermatitis herpetiformis have been reported in which there co-existed on the hands the type of dermatosis here described. It must be admitted that the character and course of the eruption are not unlike that of dermatitis herpetiformis.

Epidemic Prurigo Among Imported Asiatics. An interesting epidemic of prurigo among Annamites who had been imported into France during the war was observed by Dubreuilh.² The epidemic occurred suddenly with the appearance of forty cases in July. These cases rapidly increased until there were 116 in the hospital at one time. Later, in September, the number fell to seventeen, because the hospitals refused to accept them further.

There was practically no variation in the appearance of the various cases. Pruritis was intense and therefore led to the search for pediculi and for *Acarus scabiei*, neither of which was found in any case. Later, after the prurigo had disappeared, scabies appeared among these same people and differed in no respect from scabies in the Europeans. Therefore it is fair to assume that the epidemic of prurigo was not a mistaken scabies. The eruptions consisted of wheal-like, vesicular papules, all of which were exactly like those of prurigo or of scrofula. Some of the lesions had in the center a small papule as in prurigo but the ecchymotic points as in the louse bite never were found. Excoriations of papules resulted in a very small crust. The papules after four or five days gradually disappeared and left a brown macule, in the center of which a small scar was sometimes found. The papules were invariably disseminated and showed no tendency toward confluence. The eruption always pre-

(2) Ann. de dermat. et de syph., January, 1920.

dominated on the anterior part of the trunk, especially in the lumbar region, and formed a large belt. In some cases the eruption extended and became almost generalized but invariably respected the face, the hands, the feet and the genital organs. As a rule, the flexor poles of the extremities were spared. The distribution, therefore, is quite unlike that of scabies. As a result of the excoriation, ecthymatous lesions were numerous. The pruritus was intense and even during examination, the patient could not be prevented from scratching. Adenopathy was marked and the glands as a rule were as large as an almond. With the coming of cool weather in October, the epidemic practically ceased to exist.

The author could find no etiologic factor which would explain the development of this epidemic. There was nothing in the diet of these Asiatics which would explain the disorder. They had their own cook and practically the same food they were accustomed to with the exception of less fish than usual.

Chronic Pemphigus Vegetans. A case of chronic pemphigus vegetans which is remarkable because of the fact that it has existed for five years and the patient is still living, is reported by Barker and Carter.³ The patient was a woman 20 years old who was born in the United States but who had spent a number of years in Constantinople. She entered the hospital complaining of a skin eruption and colitis. Throughout her stay in the hospital, the colitis and gastro-intestinal symptoms were the most marked of the systemic disturbances. The lesions were typical in that they occupied the axillary and perigenital regions, and the course was marked by characteristic exacerbations and remissions. The case was seen on several occasions, was studied, and the diagnosis concurred in by Dr. Fordyce of New York. Intensive clinical and laboratory studies of the disorder failed to shed any light on the etiology of this obscure dermatosis.

Diphtheroid Bacillus in Recurrent Ulceration. A case of constantly recurring extensive ulceration of the skin was observed and studied by Barber and Knott.⁴ The

(3) Johns Hopkins Hosp. Bull., October, 1919.

(4) Brit. Jour. Dermat. and Syph., March, 1920.

authors isolated a diphtheroid bacillus which they believe to have been the causal agent in the ulceration.

[The verrucous appearance of the ulcer, as shown by the illustration, suggests blastomycosis, but the authors state that blastomyces were not present.—M.]

Guinea-Pig Dermatitis. An interesting case of severe dermatitis, the etiology of which remained for a long time unsolved, is reported by Markley.⁵ The patient was a woman of 39, who developed a severe dermatitis on several occasions; on entering the hospital, this dermatitis cleared up. Returning home, however, the dermatitis promptly recurred. After some time devoted to investigation of the possible causes of the dermatosis, it was discovered that it was due to contact with a guinea-pig which was allowed to run about her shoulders while cleaning the cage. The animal was disposed of and the dermatitis promptly disappeared. Experiments were then carried out in which it was demonstrated that a piece of guinea-pig fur applied to the skin of the patient promptly resulted in a dermatitis. An interesting feature of this dermatitis was the fact that only the sensitized skin or, in other words, the skin which had developed the dermatitis previously, was sensitive to contact with this guinea-pig fur. Other kinds of fur bound onto the skin produced no reaction. Likewise, the guinea-pig fur bound onto the skin of other individuals produced no reaction.

Pityriasis Rosea of the Scalp. The distribution of the lesions of pityriasis rosea is characteristic and of considerable value in the diagnosis of this dermatosis. The lesions usually are situated on the trunk, occasionally on the upper arm and the thigh, and in rare cases are seen on the neck and face. Up to the present time, however, probably no description of a case involving the scalp has been made. Kumer⁶ observed three cases, occurring in children between the ages of 11 and 14 years, in which the lesions were found in the scalp. The cases were carefully studied and ringworm was excluded. In the differential diagnosis he satisfies himself that the lesions in the scalp could be none other than those of pityriasis rosea.

(5) *Archiv. Dermat. and Syph.*, December, 1920.

(6) *Dermat. Zeitschr.*, July, 1920.

Cutaneous Dystrophy Following Hypothyroidism.

An interesting case in which marked changes took place in the skin following swelling of the thyroid gland in typhoid was observed by Fischl.⁷ The patient was a soldier, 38 years of age, who in the course of a very severe attack of typhoid developed a swelling of the thyroid which lasted for about two weeks. During his convalescence the skin became markedly altered in appearance. The patient became very thin and lost a considerable amount of hair, and his teeth fell out in the course of three months. The skin became very thin and is described as resembling cigarette paper in quality. The cutaneous vessels were plainly visible and there was complete absence of subcutaneous fat. The heart, lungs and the Wassermann reaction were negative, and there was no reaction to tuberculin injection. The treatment consisted in the administration of thyroid tablets. This medication was followed by remarkable improvement in the general condition of the man and in the appearance of the skin, which very rapidly returned to an appearance which was approximately normal.

Etiology of Impetigo. In a series of fifty-five cases Flehme⁸ made careful bacteriologic studies of the lesions. In all the early cases he found a pure culture of streptococcus, but in the later cases the streptococcus was sometimes associated with staphylococcus. The streptococcus appeared to be *Streptococcus longus*. It was hemolytic and developed an acid reaction in manitol-milk agar. The sediment of a bouillon culture was pathogenic for white mice, and the inoculation of the streptococcus in pure culture into the skin of men developed a typical impetigo from which the organism could be recovered in pure culture. A similar organism was recovered from the skin in 15 per cent. of cases without impetigo, and in 89 per cent. of the cases from the normal skin of patients with impetigo. The author believes that normally the intact skin has a very high resistance to the streptococcus which is found on the unchanged skin of such a large percentage of individuals. Following trauma or during epidemics the streptococcus, either by gaining entrance into the skin through the

(7) Dermat. Zeitschr., April, 1920.

(8) Ibid., September, 1920.

traumatized area or by the increased virulence of the organism, may develop an impetigo.

PARASITIC DISORDERS.

Myiasis Dermatos. Myiasis dermatosa is an infection of the skin caused by the development of larvae deposited, probably by mosquitoes, in the skin of the animal and human body. The disease is of sufficient rarity in our community to warrant the record of the case of Mook.⁹

The patient, a man aged 24, stated that he came for removal of larvae from his skin, probably the result of fly bites acquired during a visit in Yucatan, from whence he had just returned. He was in splendid health, except for the skin affection.

The two lesions he presented had appeared about six weeks before as two small red nodules, slightly pruritic but not painful. One was situated in the median line of the back over the last lumbar vertebra and the other, 3 inches to the right and 2 inches higher, in the right lumbar region. About a week previously each lesion had developed a necrotic center from which there was exuding a thin mucopurulent discharge.

At a glance each lesion resembled an ordinary furuncle with a small central necrosis. The lesions were red, inflamed, and about the size of a walnut. Close inspection revealed a moving organism which constantly plugged the necrotic opening in each lesion. The openings were about 1/16 inch in diameter. Inserting a probe gently caused the organisms to recede suddenly, apparently leaving a hollow round cavity, but, as soon as the probe was withdrawn, they immediately reappeared at the opening. The only discomfort the patient suffered was pruritus, slight pain on pressure, and great mental discomfort from the knowledge of their presence.

An incision was made under local anesthesia and each of the lesions yielded a large larva. Unfortunately they were both slightly ruptured during removal. The lesions were entirely healed within a week and the patient had no further trouble. An easier method of destruction

(9) Archiv. Dermat. and Syph., May, 1920.

would have been the application of pure phenol in the necrotic opening.

The patient stated that the parasite was known in Yucatan as the beef-worm and appears in the western part of the peninsula, particularly in the mahogany camps and in the cattle-raising region. As a rule, the larvae cause very little trouble in the natives and they treat the lesion simply by placing tobacco leaves over the opening at night and removing the dead organism by pressure the next morning.

The larvae were sent to the U. S. Bureau of Entomology and there identified by Dr. Townsend as *Dermatobia cyanivantris*.

Dr. Townsend stated that the larvae were similar in every respect to those found in the hides of cattle and that the organisms occurring in the hides caused great economic loss because of the hole produced in the leather. The mode of infestation has been proved recently to occur through the mediation of the mosquito. The eggs are attached to the body of the mosquito and hatch while the mosquito is sucking the blood of the future host.

Dermatobia Hominis. Another case of dermatobia hominis occurring in a man who had been in Central America is reported by Magath.¹

The worm which the patient himself extracted actually measured 9 mm. in length and 3 mm. in width at its greatest diameter. It was white and the rows of black hooks stood out sharply. The anterior portion was about 3 mm. in length and the posterior portion about 6 mm.

Nocardiosis Cutis Resembling Sporotrichosis. More than 300 cases of sporotrichosis have been observed and studied since Schenk reported the first case in 1898. W. H. Guy² describes a case which clinically was practically that of sporotrichosis, but from the tissue he isolated an organism which closely resembled but was not identical with the sporothrix.

The patient was a coal-miner, 50 years old. The lesion began on the left thumb and gradually other lesions appeared and formed a chain up the arm. Cultures were made from the pus and after forty-eight hours

(1) Archiv. Dermat. and Syph., December, 1920.

(2) Ibid., August, 1920.

at room temperature, there appeared on the agar several greyish white, pinhead-sized colonies, rather dense at the center which resembled a fine radiating fringe. This was found to be made up of a mass of tangled, branching threads. Older cultures showed the presence of these fine granules between the threads. The cultures were sent to Dr. W. L. Holman of the department of bacteriology of the University of Pittsburg, who said that the microörganism should be classified under the "*Actinomycetacea*." The *Actinomycetacea* is divided into two species—*Actinomyces*, including the anaërobic species, and *Nocardis*, including the common saprophytic forms, as well as a number of pathogenic species. The further classification of the nocardial strain which was given him he found practically impossible in the present state of our knowledge and the confusion of nomenclature. The morphologic picture of tangled, branching threads, granules, or spores in the threads or, in older cultures, free in the medium, the nodular appearance and the manner of growth on and in mediums, all indicated that it is closely allied to the nocardia. The presence of thread formation in the tissues without spore forms precludes its being grouped with the *Sporothrix*, *Coccidiodes* or *Blastomyces*. Further, it differs from all of these in microscopic morphology, from cultures and the type of colony developed on medium. The sporothrix is a closely allied but higher fungus with branching, septate mycelium which forms yeast-like spore bodies within and budding from the mycelium. In the tissues it shows, almost exclusively, these elongated yeast forms. The so-called spores of nocardia resemble short rods or coccoid forms of the organism and are much smaller than the yeast-like 'spores' of sporothrix. Streptothrix has been dropped from the nomenclature of these thread forms.

Immunity to *Acarus Scabiei*. Several years ago Douglas Montgomery reported the case of a patient who had a typical scabies and the person who had been sleeping constantly with this patient had not become infected. Gougerot³ has studied this subject rather extensively and makes a classification of three types. There are in-

(3) Bull. soc. franc. de dermat. et de syph., 1920.

dividuals who, when exposed to scabies by cohabitation, remain free of the disorder. They are, in other words, immune to the infection. The second type of person is the one who is immune and who does not carry the contagion. The third type is the person who is immune to the infection and yet is able to carry it to another person. For a number of years Gourgerot has made it a practice to ask the patient in all cases whether he or she sleeps with another person and whether that other person has an itching dermatosis. For a long time when the patient answered that he did sleep with another person who was free from itching dermatosis, he was inclined to doubt it but after years of observation in which the patients brought in their wives he found that these were cases in which the consort was free from lesion.

At last Gourgerot became convinced that it was possible for a patient to sleep with another person for a number of months without contaminating the other person. Under the second category he has observed a number of cases in which the mistress of one man who had scabies, abandoned that man and later took up another. She remained free from scabies and the second man was not infected. Under the third group he has observed a number of cases in which the husband who has remained free from the infection has infected either his wife or his mistress.

Mycodermatosis Due to *Mycoderma Polymoneum*. In 1912 Gougerot reported the first case of vegetating verrucous and gummatous ulceration due to this organism. The same author⁴ now reports a second case. A third, unpublished, case has also been observed by him. The patient was a man of 24, who had had the disorder for one year. Before the war the lesions were almost healed by curettage and thermo-cauterization, but there was a recurrence during the war. At the time of observation there were placards of muscle affected and squamous lesions on the right foot and popliteal fossa and the left axilla. On the hands there were cicatrices, evidently the result of suppurative eczematous lesions. Very little result follows the use of iodine. Cauterization seems to be necessary.

(4) Bull. soc. franc. de dermat. et de syph., June, 1920.

TROPICAL DERMATOSES.

Frambesia Tropica. An opportunity was given Goodman⁵ during his stay in Porto Rico and Panama, to study ten cases of frambesia tropica. He was able to demonstrate *Spirochaeta pertenuis* in many cases and found the organism morphologically indistinguishable from *Spirochaeta pallida*. The serology was investigated and all the patients gave positive Wassermann reactions. Five cases were diagnosed among 900 prostitutes. The author quotes the tabulated comparison between syphilis and frambesia tropica of Jeanselme and Rist.

COMPARISON BETWEEN SYPHILLIS AND FRAMBESIA TROPICA.

Syphilis.

1. Disease pandemic.
2. Acquired by heredity and contagion.
3. Begins by a primary pathognomic lesion at point of inoculation.
4. Immunity conferred by syphilis is in a sense permanent.
5. All attempts at auto-inoculation of a patient with secondary or tertiary syphilis are fruitless.
6. The hard chancre and other signs of syphilis can appear on a subject who may have yaws.
7. The polymorphism of syphilitic manifestations.
8. Syphilides, at least those of the tertiary period destroy the skin, and leave after cure permanent scars.
9. Syphilis is an infection in which the several lesions correspond to three periods, primary, secondary and tertiary.
10. Syphilitic eruption involves mucous membranes.
11. Localization in the viscera.

Frambesia Tropica.

1. Disease tropical.
2. Acquired only by contagion.
3. Initial lesion near portal of entry is not constant nor different from lesions appearing later.
4. Re-inoculation of yaws is possible.
5. The auto-inoculation of yaws is possible for an indefinite, but quite long period.
6. Yaws can develop on a subject with syphilis.
7. Monotony of eruption; papillomatous only.
8. Frambesial lesion which is not exposed to any irritation heals without leaving a trace.
9. All the manifestations of yaws are identical, whatever their date.
10. Frambesia lesions do not involve mucous membranes.
11. No localization in the viscera.

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|-------------------------------------|--|
| 12. Syphilides are not pruriginous. | 12. Yaw lesions are accompanied by lively itching. |
| 13. Alopecia in secondary period. | 13. No alopecia in the course of the disease. |

Treatment with arsenobenzol (arsphenamine) and nov-arsenobillon (neo-arsphenamine) in the hands of the author gives the usual beneficial results described by others. Goodman is inclined to the belief in the dual character of frambesia tropica and syphilis on clinical grounds alone. The extensive evidence accumulated in confirmatory to non-identity of the two diseases.

Report of Case of Frambesia Tropica. A case of frambesia tropica which was carefully studied is recorded by Cassar.⁶ An interesting feature of the case was that although the organisms were found in great number, the organisms could not be inoculated successfully into the rabbit or into the guinea-pig. The blood Wassermann was positive and the lesions disappeared promptly after administration of neo-arsphenamine. There were definite changes in the cerebrospinal fluid. The spinal fluid cleared up after intravenous therapy. So far as Cassar is aware this is the first time that changes have been noted in the cerebrospinal fluid in frambesia tropica.

Gale Filarienne or Craw-Craw. "Craw-craw" is a term used by the natives of the west African coast to designate several diseases of the skin, including ring-worm, scabies and eczema and other dermatoses of various types occurring in the negro.

Montpellier and Lacroix⁷ observed a large group presenting symptoms closely simulating those of scabies. However, examination for *Acarus scabiei* was negative. Moreover the distribution of the lesions differed essentially from those of scabies. Further examination disclosed the fact that the parasitic organism was a micro-filaria. It was found to occur in the papillary bodies and the subpapillary region of the derma. It was never found in the epidermis. As a rule it was elongated and somewhat undulated and in some cases it was more or less rolled upon itself. It existed in the connective tissue absolutely independent of the vascular tissue of the papillae or the subpapillary plexus of the vessels. The organisms caused very little local inflammatory reaction

(6) Ann. de dermat. et de syph., 1919, p. 462.

(7) BuH. soc. franc. de dermat. et de syph., 1920, No. 3.

of the tissue. Considerable difficulty was experienced in obtaining these organisms but finally it was found that the best method of obtaining them was by biopsy. In the opinion of the author, these microfilarial organisms are the embryos of *Filaria volvulus*.

The cutaneous lesions are characterized by small papules only slightly elevated and a condition of what is termed pseudo-lichenification. There are also papulovesicles and vesiculo-pustules in different stages of evolution.

Differential diagnosis between this and scabies is not difficult because the region usually involved in scabies is almost invariably spared in this dermatosis.

MUCUOUS MEMBRANE DISORDERS.

Burning Tongue. A series of eleven cases of burning tongue has been observed by Engman.⁸ Of the eleven cases, nine were in females and the age ranged from 35 to 65 years. No one of the patients had any pathologic changes on the tongue except enlarged papillae from constant feeling for the sensation against the teeth and all the patients appeared in an almost terror-stricken condition for fear of carcinoma of the tongue.

The first case, which is typical of all the others, occurred in a woman 35 years old, who noticed while riding on interurban car one day, a peculiar burning or scalding sensation on the anterior portion of the tongue. She thought that she had probably unconsciously taken something too hot but did not at the time remember having burned her tongue in this way. It worried her so much that she consulted her physician, without benefit. Her mind at once centered itself on the fear of cancer and the possibility that this burning sensation might be a forerunner of malignancy.

The other ten cases have substantially the same history as the foregoing, with only a few variations. Sometimes the condition is limited to the tongue and the central portion of the lower lip. The sensation is one of burning and hyperesthesia on touching the tongue with a pin or some examining instrument. There are no objective symptoms. In several cases, however, local

(8) Archiv. Dermat. and Syph., February, 1920.

PLATE V.



Neurotic excoriations.—MacKee, page 50.

PLATE VI.



Neurotic excoriations, showing disfiguring, scarring eruption.—
Pusey and Senear, page 54.

changes have been produced by painting the tongue with various reducing agents, such as silver nitrate, and potassium chromate.

The treatment consisted in an attempt to convince the patients that there were no pathologic process going on which would eventuate in epitheliomatous transformation. The author believes that a suggestion made by Sluder that the sensation in the tongue may be produced by inflammation in the lingual tonsil on either side may be a factor in the production of the burning tongue described by him. Since reading the statement by Sluder, Engman has not had the opportunity to examine any one of the eleven cases observed, and therefore, the condition of the lingual tonsils is not known.

Papillomata of the Buccal Mucosa. In 1919, Lévy-Bing and Gerbay⁹ described the occurrence of a large group of papillomata on the buccal mucous membrane of an Arab. In this article, Jamin¹ describes a similar case which occurred in a native of Tunis. He says that this is rather a common condition among the natives of this country. The papillomata occupied the entire interdental line on the left and spread out over the vermilion border of both lips and to the labial commissure on the right, at which point they were considerably pedunculated whereas on the left they were flat. The lesions included flat warts of the juvenile type, verruca vulgaris, and the condyloma acuminatum. On the hands were many lesions of verrucae vulgaris. There were no anal condylomata, however.

Monilia Candida Infection of the Mouth. An interesting case of infection of the mouth by a fungus which has been identified by Professor Moore of the Missouri Botanical Gardens as the *Soorpilze* of Plaut was studied by Engman and Weiss.² The patient was a laborer, 53 years old, who had had the disorder for seven years. The lesions covered the entire left side of the buccal mucous membrane and appeared as a thickened mass of whitish, filiform projections which was sharply defined against the healthy mucous membrane. The appearance of the entire lesion was peculiar, looking at first glance

(9) Practical Medicine Series, 1919, Vol. VII, p. 123.

(1) Ann. des mal. vén., May, 1920.

(2) Archiv. Dermat. and Syph., February, 1920.

like a form of leukoplakia. It mounted to the hard palate, sweeping over it and throwing out a peninsular extension to the right side and extended backward to the left pillar of the fauces. Here it was fissured, particularly at the angle of the mouth and at the junction of the buccal mucous membrane with the ramus of the jaw. All the teeth of the left side of the lower jaw had been extracted. The peculiar appearance of the lesion could be described best as a "frozen doormat" appearance, *i. e.*, a doormat covered with frozen moisture as is frequently seen in the winter; the white filiform projections were thickly matted and of a white glistening appearance on a whitish macerated base.

Scrapings from the lesion, prepared with potassium hydroxide in the usual way, disclosed a peculiar fungus which at first was thought to be some variety of the trichophyton group, but which was later identified as the *Scoorpiæ* of Plaut. The fungus was constantly found and was so firmly engrafted on the lesion that it had to be considered as the probable etiologic factor. No antiseptic mouth washes or applications affected its growth in any way. No biopsy was made. The Wassermann reaction was negative and there was no history of syphilis.

As no local treatment seemed to affect the progress of the condition, the patient was anesthetized and the whole area was cauterized, which did not seem to delay the peripheral extension of the process; in fact, it seemed to accelerate rather than to retard it. Eventually the patient developed a carcinoma in the area and operative procedure was resorted to, resulting in the removal of the greater part of the lower jaw.

CUTANEOUS NEUROSES.

Neurotic Excoriations. An interesting paper by MacKee³ in which he reviews the literature and reports a number of cases was read by him before the Section on Dermatology of the American Medical Association in 1919.

(3) *Archiv. Dermat. and Syph.*, March, 1920.

The modern use of the term neurotic excoriations is limited to traumatic lesions produced by a person without intent to deceive. Some of these persons appear to possess normal nervous systems; most of them are more or less neurotic, and a few are hysterical. The affection is more common in females than in males. It is usually encountered between the ages of 18 and 50.

At times the excoriations may be produced by the habit of picking at every slight elevation on the skin. This picking or digging may be quite unintentional and, in mild cases, it is limited to an unconscious habit of passing the hand over the face (and the scalp, if bald) while deeply absorbed in study, locating a little follicular plug and digging with the finger nail until an excoriation is effected. In the same way the reparative crust is repeatedly removed, healing is retarded and the lesion may persist for weeks or months, becoming perhaps indurated or infected and, finally, when left alone, disappearing spontaneously, often with scar formation. In these mild instances the habit, which is really unconscious, is overcome by remonstrances by members of the family before much harm is done (Plate V).

In the more pronounced cases the habit is not controllable and the person finds it difficult, if not impossible, to avoid picking at little islands of epithelial debris, follicular plugs, comedones, stubby hairs, acne lesions, milia, and crusts. The point to be emphasized in this type is that the patient has no reason, other than a nervous habit, for interfering with Nature. It is the same kind of impulse that makes one bite the nails, chew the mustache, bite the lips, and suck the thumb.

Another type is that in which the person has a mania for picking at lesions of various kinds for the purpose of promoting healing, to remove supposed foreign bodies and insects. Unlike the former type there is here a definite reason for the act. As an illustration, a person becomes convinced that a milium body contains an insect. The lesion is opened and part of its contents removed, considerable excoriation being produced. A scab quickly forms, the uncomfortable feeling of which is supposed to indicate that the cause has not been overcome. The scab

is then removed and little pieces of fibrous tissue and a little serum is obtained by picking and squeezing. Temporary mental rest is obtained, but soon the lesion feels again uncomfortable and the process is repeated over and over again until unsightly ulcers and scars are produced. The point to be emphasized here is that the person purposely injures the skin and has a definite reason for so doing, but there is no effort to deceive.

There is still another type of excoriation, namely that associated with chronic itching dermatoses such as dermatitis herpetiformis, prurigo, chronic urticaria and pediculosis. Here, however, there is no habit or mania, but simply vigorous attempts at relief from severe itching. Such cases can not be classified as neurotic excoriations. On the other hand, there are neurotic individuals in whom the itching accompanying a mild urticaria or pruritus is markedly intensified by the peculiar temperament, and in whom the scratching and digging is entirely out of proportion to the subjective symptoms. Such cases can very properly be classified under neurotic excoriations—a secondary type.

Different persons have various reasons for injuring the skin, and this has led to the use of a number of terms in an attempt at dermatologic designation. E. Wilson was the first to employ the term neurotic excoriations. Under this heading, as pointed out by Adamson, he included not only cases similar to the foregoing, but excoriations in hysterical women produced by rubbing with intent to deceive—true malingering. It is essential that a clear distinction be made between these two affections. Malingering (dermatitis factitia, dermatitis artefacta, dermatitis ficta, feigned eruptions) is production of lesions by friction, with acids or in other ways and the denial of the act. The lesions are produced for the purpose of avoiding work, or of exciting sympathy. In the neurotic excoriations, the patients may be unable to overcome the habit, but they readily admit the self-infliction of the lesions and will always explain the reason, sometimes at great length and detail. There is never any attempt at deception and no effort to excite sympathy or to avoid work. In fact, most of these individuals earnestly welcome an attempt to aid them in overcoming the habit.

The name "acne urticata" was proposed by Kaposi to indicate a condition in which wheals and pruritic papules occur in neurotic persons and in which the incessant rubbing and scratching results in excoriations. Adamson, in discussing Kaposi's cases, makes a very good point when he suggests that the wheals and the papules instead of being primary, may be secondary to the rubbing. The famous dug-out cases of Colcott Fox probably belong to this group. Whether or not these cases are really a form of urticaria, prurigo or some other affection, the facts are that there is itching which is either very severe or that slight itching is extremely annoying to the neurotic and even hysterical person, and that the excoriations and ulcers are produced in mild attempts to relieve the symptoms.

In addition to the types already discussed, must be mentioned several other conditions that are not infrequently associated with excoriations and ulcers. Acarophobia is the condition in which the patient is convinced that he is infested with insects. There may be no lesions, but the individual will collect tiny particles of wool or cotton adhering to the skin, epithelial debris and even extraneous insects and exhibit them to the physician. In attempting to destroy and collect these supposed insects or to relieve imaginary symptoms produced by them, the skin is likely to be injured. Similar lesions may occur when extracting or breaking the hairs in trichotillomania (Besnier) and in trichokryptomania (Sutton). The term "*dermatothalasia*" was employed by Fournier to indicate a mania for scratching and rubbing various parts of the body to the point of excoriation. Also in the literature one finds the terms "dermatitis gangrenosa," "pemphigus hystericus," "urticaria necrotisans" and several others, but they all designate one of two types—either malingering or neurotic excoriations.

The question of differential diagnosis is important. A perusal of the illustrative cases reported shows that neurotic excoriations may markedly simulate syphilis, tuberculosis, radiodermatitis, dermatitis herpetiformis, acne varioliformis, and other dermatoses. Care also must be taken to differentiate clearly between neurotic excoriations and malingering, and to exclude excoriations pro-

duced in attempts to relieve severe itching by individuals who are not neurotic.

Another group of three cases of neurotic excoriation is reported by Pusey and Senear.⁴ Reviewing the literature they find that the cases fall into three groups as follows:

1. Neurotic excoriations (Wilson); dug-out excoriations (Colcott Fox).

2. Acne urticata (Kaposi); urticaria necrotisans (Waelsch).

3. Excoriated acne of young women (Brocq).

The neurotic excoriations of Wilson and the dug-out excoriations of Colcott Fox have a common origin; that is, the lesions are produced by rubbing the skin with the finger tips or scratching it with the finger nails.

The history of the case usually is that the patients have had their attention drawn to the skin by some disturbance of sensation, usually itching, or by the presence of an actual itching lesion, and the tendency to scratch or rub or otherwise injure the skin at these sites thus produced has developed into an irresistible impulse, so that excoriation after excoriation is produced from day to day. Details of numerous cases of this sort are found in the experience of Wilson, Fox, Adamson and others.

The common lesion in these cases consists of an oval excoriation, usually slightly elongated and about the width of a finger tip. As a rule, the excoriations are crusted, and many of the cases show pigmented spots or atrophic scars, the result of healed lesions. The British authors have been divided on the question of the etiology, some maintaining that in all cases a pruritic dermatosis preceded the excoriation, while others maintained that this was not true in all (Plate VI).

The acne urticata of Kaposi less surely belongs to this group. Kaposi seems to have understood the character of these cases more clearly than most of his successors, for he calls attention to them as occurring as "wheal-like" lesions, and to the fact that the damage to the skin is produced by self-inflation. But the name that he gave it, "acne urticata," is inept. As Kaposi intimated, the lesions occur as wheals; Waelsch con-

(4) Archiv. Dermat. and Syph., March, 1920.

cluded that the disease is "a chronic recurrent urticaria with superficial necrosis." Many other observers also have called attention to the urticarial character of the lesions. A better name for the condition would likely be "urticaria necrotisans," as suggested by Waelsch. Numerous observers have reported necrosis in this condition as spontaneous, but Adamson suggests that the necrosis in these cases is traumatic and a result of self-infliction.

The excoriated acne of young women, of Brocq (*l'acné excoriée des jeunes filles*), is the condition seen in a moderate degree very frequently in young women with acne, who develop, through their anxiety over their disfigurement and their effort to cure their lesions, a nervous habit of producing excoriations in the skin by digging at the lesions. There is more or less of a nervous element in these cases, but it does not amount to a neurosis.

The cases presented by Pusey and Senear do not fall exactly into any of these groups but are essentially of the same character as the cases of neurotic excoriations of Fox and Wilson.

A Borderline Case of Neurotic Excoriations. A case presenting some of the features of both dermatitis facititia and neurotic excoriations is described by Pusey.⁵ The patient was a woman of 26, a nurse, who acted as an attendant in a physician's office. Some time before coming under observation, she had burned her hand with the resulting superficial scar over the dorsum. In spite of local soothing applications, the lesion persisted for more than a year. When seen by Pusey, the appearance of the eruption was not that of the ordinary feigned eruption but neither did it resemble any known dermatosis. The individual lesions were such as might be produced by local injury combined with simple pus infection. It was not difficult, therefore, to arrive at the conclusion that the injury was probably self-produced. The patient did not present the usual facies of the malingerer. She was alert, looked one in the eye and answered questions without evasion. When the opinion was given that the lesions were self-produced the doctor frankly said that he could not believe it. The woman,

(5) Archiv. Dermat. and Syph., September, 1920.

however, readily admitted that this might be true, as she found herself constantly picking at the hand and could not avoid it. She was not secretive nor was she on the defensive. If she was doing it it was through a nervous impulse which she had not been able to resist, and she was ready to coöperate with Pusey in meeting the situation. The treatment consisted of weak aluminum acetate solution compresses and an occlusive dressing under which the lesions promptly healed in the course of two and a half weeks. During the night the hand of the patient was protected in order that she could not traumatize it during sleep.

So-called Dermatitis Dysmenorrhoea. Since the report of Matzenauer and Polland on "*dermatitis symmetrica dysmenorrhoea*," a number of articles have appeared in which similar cases have been reported. Many of these cases have been obviously cases of dermatitis factitia or self-inflicted eruptions. Wise and Parkhurst,⁶ however, report a case which they are convinced is a genuine case of dermatitis dysmenorrhoea, inasmuch as it appeared during the menstrual period and completely subsided in the interim. Moreover, it cleared up during gestation. The authors satisfied themselves that self-infliction, malingering, and neurotic excoriations played no part whatever in the causation of this dermatosis (Plate VII).

Purpura Factitia. A case of purpura factitia which is interesting because of the manner of production is reported by McKeown.⁷

A girl of 13 was admitted to hospital on April 22, 1920, for "purpura," when she gave the following history:

On April 17, she had not felt well, had vomited once and had complained of pains in both arms. She stated that large purple patches, not painful on pressure, had appeared all over her arms and legs on the same evening, and that her elder sister had had similar patches all over her body some years before. No history of rheumatism was obtained. The patient belonged to people in extremely poor circumstances and was rather hysterical in type.

(6) Archiv. Dermat. and Syph., December, 1920.

(7) Lancet, Sept. 11, 1920.

The temperature, pulse and respiration were normal. On examination there were seven large purpuric patches, varying in size but not in shape, on the flexor surface of both arms and forearms, with three similar patches on the legs. The highest patch on the right side was on a level with the tip of the acromion process. The patches on the legs were on the inner and outer surfaces, midway between the knee and ankle. The patches consisted of numerous minute hemorrhagic spots and petechiae set closely together and presenting a definite grouping. There was an outer band representing the outline of an oval and two straight lines somewhat broken running along the long axis. All the patches with the exception of two were oval, measured 2 in. by 1 in., and were very sharply defined. The two exceptions were on the arms and were linear, starting on the extensor surface and coming round to the flexor surface. The rest of the physical examination was negative.

At a first glance purpura was suggested, but a suspicion of self-infliction was aroused by the similarity in shape and size of the majority of the patches, the strange shape, the position and distribution, and lastly, the absence of any purpuric manifestation elsewhere.

During the first examination it was easily shown that all the marks occurred on places accessible to the patient's mouth, and later they were able to prove experimentally that similar patches could be produced by taking hold of a piece of skin with the teeth and then applying strong suction with the lips. The existing patches were ringed with silver nitrate, and the patient was given ample opportunities for producing fresh ones, but none appeared. After three days the patches became brown in color and faded in a week.

DISEASES OF THE NAILS.

Onychauxis Due to Hypopituitarism. An interesting case of onychauxis due to hypopituitarism is reported by Hollander⁸ of Pittsburgh. The patient was a small boy 10 years old, who was referred to Hollander on

(8) *Archiv. Dermat. and Syph.*, July, 1920.

account of the formation of the finger nails. This formation had existed practically since his birth, with constantly progressing changes. The nails appeared to show a hypertrophy in breadth and thickness and were changed in color, texture and density. All nails were involved, though the process originally started on the nails of the great toes, and gradually involved all the toes and fingers. The most marked changes were noted in the nails of the great toes. These were much thicker than normal and the upper surface was grooved by the



Fig. 1. Congenital unguis atrophy.

uneven piling up of nail substances, giving them a transversely striated appearance. The grooves could be distinctly felt and gave the nails a rough feel. The nails were lusterless and were brown, dark brown or black. The older the involvement the darker the color of the nails. The patient had an abnormal appetite and frequent attacks of nausea followed by vomiting. These always occurred at night and were followed by severe headache of the migraine type. The attacks were of three years' duration and were constantly becoming more frequent. The boy complained of difficulty in vision at times, with considerable blurring of letters. He was also troubled with occasional epileptiform seizures of the *petit mal* type. The patient's general appearance con-

sisted of a marked feminine character of the breast and broad pelvis, a slight suggestion of genu-valgum, a dry skin and hair, and absence of signs of axillary or pubic hair, small genitalia, and highly arched palate. The Roentgen-ray showed a small sella turica, with hypertrophy of the anterior and posterior clinoid processes. The boy's apparently high carbohydrate tolerance led to the conclusion that this was a case of hypopituitarism, and that the trophic changes occurring in the nails could be chiefly attributed to this cause. Optic atrophy, which examination of his eyes revealed, was not due to the hypopituitarism and Hollander states that a trial of antisyphilitic medication should be made.

Congenital Atrophy of the Nails. An unusual case of congenital atrophy of all the nails of the hands and feet is reported by Lutembacher.⁹ The nails were all exactly alike and were in the form of a small square about 3 mm. on each side. The nails had no free border and were enclosed completely in tissue all about the four sides. The surface of the nails was somewhat uneven but the color was approximately normal except that there were a few areas of a whitish appearance. The fingers were short and thick. The distal phalanx presented some hyperextension probably because the top of the finger-tip where it came in contact with objects was turned back, owing to the lack of support from the nail (Fig. 1). The patient was a woman 40 years old who was a seven-months child and who had a skin that was of a xerodermic type. The skin was very dry and somewhat scaly. While still under observation, she developed a typical case of lichen planus.

DERMATOMYCOSES.

Trichophytia Profunda (Kerion Celsi). Some interesting clinical, cultural, immunologic and therapeutic observations on kerion celsi have been made by C. Rasch¹⁰ of Copenhagen, who had the opportunity of studying a large series of cases.

(9) *Ann. de dermat. et de syph.*, October, 1920.

(10) *Brit. Jour. Derm. and Syph.*, November, 1920.

In 1911 Jadassohn made the clinical observation that patients with *T. profunda* often had an eruption resembling, more or less, *lichen scrofulosorum*, the so-called lichenoid trichophytides—an observation which has since been confirmed by various observers.

Experiments with animals explain the long-known fact that the most severe form—*T. profunda* (kerion)—accompanied by inflammation and swelling, is most quickly and easily cured, while the “lightest” most superficial cases take the longest time. With the first occurs a complete change in the organism by the formation of an abundance of matter which secures immunity, whereas the latter affections, which are only found on the epidermis and in the hair, do not set up enough local reaction to produce the formation of this matter.

The author's cases show that with *Trichophytia profunda* several other eruptions occasioned by this disease are found in addition to Jadassohn's lichenoid eruption. During the years from 1912 till June, 1919, 109 cases of trichophytia have been treated there in the hospital. Of these cases, seventy-one were accompanied by kerion formation, and fifty-one were localized in the hair of the head and twenty in the region of the beard. Culture was undertaken in only about half of the cases. As regards the cases found in the scalp, *Trichophyton faviforme discoides* was found most frequently (thirteen times), *T. violaceum* grew twice, and *T. gypsum asteriodes* twice. No fungus grew from a number of the cases; most of these, however, are probably due to *T. faviforme discoides*, from which it is often difficult to produce cultures. As regards the cases in the beard, *T. faviforme discoides* was found four times, *T. plicatile* twice, the very closely allied *T. cerebriforme* twice, *T. gypsum asteriodes* once, and *T. rosaceum* once.

Granuloma trichophyticum (Majocchi) was found four times; in two of these cases successful cultures of *T. plicatile* were found.

In nineteen of the patients (all children) the papular eruption, the so-called lichenoid trichophytides described by Jadassohn in 1911, occurred, sometimes combined with spinulous, vesicular or pustular formations. In six cases in which the fungus was grown it was found to be the

T. faviforme discoides. This eruption is extraordinarily varied in its distribution, quantity, and grouping. Sometimes only single, small, pink, scattered, follicular papules are found on the body, extremities, or the face; sometimes it covers the entire skin with thousands of individual lesions, while in between are found all transitions. Sometimes the papules are distributed without any visible order; at other times they are grouped more or less regularly. The so-called corymbiform formation, as described by Inga Saeves, was seen twice. At times the papules stand isolated on normal skin, and at others they are surrounded by a more or less extensive flushing of the skin. The large lesions are almost always accompanied by fever.

In addition to this papular lichenoid eruption the cases have shown that various other forms secondary to the kerion formation are also seen. Thus pure vesicular eruptions generally consisting of purulent vesicles the size of a pin's head were found five times. This eruption was found once in large groups on the buttocks, once on the toes, and once distributed on the arms. In this last case the vesicles were surrounded by a broad red halo, which in several places converged into large irregular erythematous patches. Finally, this eruption was found twice on the scalp and parts of the forehead and temples (Plate VIII A).

A scarlatiniform eruption was seen twice. Such scarlatiniform eruptions with kerion seem only to have been observed once before, for Jadassohn says that it may come to an eruption well-nigh resembling scarlatina, without, however, giving any history of the disease. These erythemas should be borne in mind when the differential diagnosis of scarlatina is being considered. They do not seem to be particularly rare, as in the author's fifty-one cases of kerion of the scalp they occur twice. No doubt they will always be accompanied or, in the course of a few days, be succeeded, by a positive trichophytin reaction (Plate VIII B).

In five cases in the scalp, after kerion had already existed for some time, a very extensive desquamation was found, resembling pityriasis simplex, with a deposit of dense, white, or greyish yellow scales, with a very uni-

form dissemination over the entire circumference of the hairy scalp. In some of the cases it seems to arise secondarily to the previously mentioned vesicular outbreaks. Another form of scaling trichophytides is the minimal (pseudo-psoriasis) scale formation, which, with these patients, sometimes occurs on the knees or other places.

Kerion celsi also seems to be capable of causing erythema nodosum, resembling nodes on the shin-bones such as B. Bloch and L. Pulvermacher (1919) have seen with kerion patients who also had lichenoid trichophytides. No such case was found in this series.

The treatment of kerion consisted of boiled water fomentations only, which were changed from four to six times in the twenty-four hours. Under this treatment pain and swelling quickly abate, and in the majority of cases no other treatment is called for. It is a peculiar and interesting fact that fomentation dermatitis has never been observed in these cases. Incision is quite improper, as Tilbury Fox has already pointed out; it is harmful because the large open wounds occasioned by incision take an extremely long time to heal. If there is retention of pus one or more small punctures by galvanocautery can be successfully employed—a treatment which also is generally successful with cases of local deep nodes found with granuloma trichophyticum. Under the fomentation treatment all the cases healed in the course of from three to six weeks, and, what is of importance both theoretically and practically, *all other foci of trichophytia on the skin disappeared simultaneously without any local treatment whatsoever.* It likewise invariably appears that the change in the organism caused by the kerion lesion, which generally takes place accompanied by fever and general indisposition, has the immediate effect that the skin becomes immune, so that no new inoculations appear. This healing effect of kerion on all the other simultaneously existing trichophytic lesions and its ability immediately to prevent fresh inoculations does not seem to have been previously mentioned. This clinical observation agrees very well with the results attained by experiments on animals. Whether this circumstance is identical in all cases of kerion it is of course impossible to say; it is invariable with the kerion lesions

caused by *Trichophyton faviforme discoides*. As the immunization, or autovaccination is due to a strong production of trichophytin in the kerion spots, the often proposed trichophytin treatment seems to be superfluous in these cases.

When one has seen this great healing power which lies in the kerion lesion, and when one knows that this influence is not specific to the individual kind of trichophyton, but is applicable to most, if not all, kinds of trichophyton, one is strongly tempted to utilize it for curative purposes with cases of superficial chronic kinds of trichophytia, such as *T. violaceum* which are not accompanied by inflammation, the curing of which may, in spite of Roentgen treatment, take months or years. It is highly probable that a kerion caused by an inoculated *T. faviforme* will be able to master these affections in the course of about two months. Even in 1910 Sabourard (*Les Teignes*) stated that a kerion could protect against favus, and considered it possible that one would be able to cure favus by an artificially produced kerion; there is, however, no record of any such attempt having been made. In Rasch's opinion, it would be rational and fully justifiable to employ this treatment in suitable cases.

[At a meeting of the St. Louis Dermatological Society in November, 1920, Engman demonstrated cases of kerion due to large spored fungi which had promptly yielded to intravenous injections of typhoid vaccine. The patient was hospitalized and the injections were given every other day. The temperature rose to 103° and 105° F. but the patient suffered no ill consequences. The therapeutic results were remarkably good.—M.]

The Pathogenesis of Trichophytide. A remarkable case, which is probably the first one thus far recorded of trichophytide, in which it was demonstrated culturally that the trichophytide was hematogenous, is reported by Sutter.¹ The patient was a girl 10 years old, who had been in contact with horses having ringworm for some time. She developed ringworm of the scalp which in the course of about three weeks became rapidly transformed into kerion celsi. During this time the regional lymph glands became markedly enlarged and the

(1) Archiv. Dermat. and Syph., February, 1920.

child lost appetite and weight. About two weeks after the development of the kerion the girl became quite ill and manifested prodromal symptoms resembling those of an infectious exanthem. She suffered from headache, vomited and developed chills and fever. The temperature reached 39.5°C ., and over the entire body a bright red scarlatiniform rash appeared. The prodromal symptoms, the high temperature and the rash made the diagnosis of scarlet fever seem most probable. There was marked generalized adenopathy and a palpable spleen. About twenty-four hours after the onset of the exanthem the temperature dropped to normal and the exanthem became transformed into a fine, papulo-follicular eruption which in places was confluent and developed scales simulating a seborrheic psoriasiform patch. About this time an acute arthritis developed in a number of the large joints. Puncture of the lymph glands gave a pure culture of *Trichophyton granulosum*, which was the same organism recovered from the kerion celsi and from the follicular cutaneous lesions.

Penicillium Breviceale in a Case of Ringworm of the Toe Nails. A case of ringworm of three toe nails on two feet is described by Weidman², in which the scrapings were studied microscopically and cultivated. Spores resembling mycelia and blastomyces were found in scrapings, and nine different species of fungi were isolated in cultures. Among the fungi a coco-brown penicillium was isolated, but as it was only cultivated once out of three trials, and produced no disease on injection into animals and inoculation on the skin, the author is inclined to question its pathogenicity. Weidman believes that *Penicillium breviceale* is the only pathogenic organism in this group.

Two Unusual Cases of Ringworm. Two cases of ringworm which were unusual because of the duration and extent of the lesions and because of the unusual clinical appearances are reported by Hartzell.³

The first case occurred in a man, 30 years old, who had an eruption consisting of papules and nodules varying in size from that of a hemp seed to that of a split pea, oc-

(2) Archiv. Dermat. and Syph., December, 1920.

(3) Ibid., January, 1920.

PLATE VII.



Dermatitis dysmenorrheica on the fifth day of the menstrual period.—Wise and Parkhurst, page 56.

PLATE VIII.



A.—Vesicular trichophytides (kerion of the scalp).



B.—Scattered trichophytic elements; universal scarlatiniform erythema (kerion of the scalp).—Rasch, page 59.

cupying the region of the right deltoid and the greater part of the right side of the trunk. The lesions were dark red and for the most part discrete. They were most abundant about the posterior borders of a large moderately pigmented area in which were a few scattered nodules and small superficial scars and many of them had small blood crusts on their summits. It was quite evident that the disease was slowly extending backward toward the spinal column; the pigmented parts represented areas over which it had already passed. The patient first stated that the duration of the disease had been three years but further questioning brought out the fact that five years before there had been little rings on the chest which gave him no concern; only in the past three years had the eruption spread extensively and caused annoyance. In addition to the affection of the skin, the nails of the index, middle and ring fingers of the right hand presented marked evidence of disease. Scrapings taken from the skin and nails showed an abundance of mycelium presenting the morphologic characters of a trichophyton. No culture was made in this case.

The second case occurred in an Austrian 28 years of age who presented a number of dark red slightly pigmented round and oval patches varying in size from that of a coin to that of a hand, situated over the crest of the left ilium, in the pubes, on the buttocks, on the posterior surface of the thighs and in the left popliteal space. The margins of these patches were decidedly elevated and their surfaces were covered with a scanty, fine, bran-like scale. In addition to these patches, there were a number of brownish-red shot-sized nodules with hard crusts on the stomach and scattered about on the posterior surface of the left thigh in the neighborhood of the large popliteal patch. The disease had lasted about eight months and was still extending. Under local treatment, which consisted of the application of a 2 per cent. solution of salicylic acid in alcohol, the eruption rapidly disappeared and at the end of three weeks nothing remained but a brown pigmentation.

Cultures made from the organisms found in the tissue of this case presented characteristics which led Hartzell to identify the organism as "*Trichophyton rosaceum*."

Histologically nothing was found but a well-marked follicular keratosis.

Eczema Marginatum of Flat Surfaces. In 1919 we recorded in these volumes the work and observation of Pautrier and of White concerning the invasion of flat surfaces by *Epidermophyton inguinale*. In this article Malherbe⁴ reports two cases occurring in man and wife in which the infection took place first in the man and was subsequently conveyed to the wife. In both cases the eruption resisted treatment for a long period of time and constantly recurred. In both considerable eczematization occurred before the disorder yielded to applications. This is further proof that these organisms not infrequently invade the surface which are flat and quite beyond the cutaneous folds.

Microsporon Audouini in Algiers. In 1907 Joppe stated that *Microsporon Audouini* did not exist in Algiers. In 1919, Montpellier stated that after considerable experience he had never encountered it. In this article, however, he states that he has discovered one case.⁵ The lesions were typical clinically, microscopically and culturally.

Cultivation of Epidermophyton Inguinale. A plate method for making cultures of *Epidermophyton inguinale* is described by D. L. Farley⁶ of the University of Pennsylvania.

Melted agar medium, cooled to 45° C., is allowed to run slowly from a pipet into a Petri dish so that an area of hardened medium is formed in the center of the dish, leaving a zone free of medium about it. The object of this is to prevent secondary contamination from creeping in from the edges, as so often happens when the entire area of the floor of the Petri dish is filled with medium. After the agar is well hardened the dish is inverted, the lid removed and the half containing the medium carefully placed on a sterile glass plate 8x6 inches. Melted paraffin is then painted around the contact surface of the plate and Petri dish with a small brush, thus sealing the chamber. Before planting these, modified Petri

(4) Ann. de dermat. et de syph., 1920, p. 205.

(5) Bull. soc. franc. de dermat. et de syph., April, 1920.

(6) Archiv. Dermat. and Syph., October, 1920.

dishes are allowed to incubate at room temperature for a few days to insure their sterility.

[In a conversation with Sabouraud in his laboratory disapproval was expressed of this method of making cultures. A small amount of agar contained in a relatively large Petri dish chamber allows it to dry out quickly and, moreover, there is not enough surface on which the colonies may develop freely. The preparation of these Petri dishes would appear to be rather difficult and access to them would necessitate melting the paraffin and removing the plate. In my own work I have found the use of a whisky flask very satisfactory in every way. The flasks are cheap now that the 18th Amendment is operating; they are easy to prepare and a small amount of non-absorbent cotton serves as a stopper. From eight to twelve pieces of tissue may be planted in one flask.—M.]

Gentian Violet as the Restrainer in the Isolation of Fungi. The work of Churchman on gentian violet has shown that this substance possesses a peculiar quality of inhibiting in high dilution the growth of gram-positive organisms. D. L. Farley⁷ of the University of Pennsylvania, has made use of this in the cultivation of fungi from cutaneous tissue. It was found that a dilution of gentian violet of 1:500,000 in Sabouraud's media would inhibit the growth of the Gram-positive bacteria. It was found also that fifty-one strains of fungi would grow freely on maltose media containing gentian violet in a concentration of 1:250,000. This gentian violet restrainer was used in the isolation of about twenty strains of pathogenic molds with apparently good results.

[In my own work with the pathogenic fungi I have encountered very little difficulty with contaminating Gram-positive bacilli. The use of 95 per cent. alcohol, or flaming the tissue seems to be all that is required inasmuch as all Gram-positive bacilli do not grow luxuriantly at room temperature. The most troublesome organism is *Penicillium* which in the experiment of Farley invariably was found to grow through all concentrations and with no evident impairment even in gentian-violet concentrations of 1:1000. Therefore, the method is of least value as a restrainer when most needed.—M.]

(7) Archiv. Dermat. and Syph., October, 1920.

Spore Identification in Scrapings. The identification of spores in hairs and in tissue scrapings is not always a simple matter, particularly if there be only a few spores present. Bachman⁷ found that by passing the spores through heat on a coverslip they became scorched to a brown and that they then contained reddish refractile granules which gave them a characteristic appearance. When identifying the spores in tissue, the tissue should be teased to very small pieces with dissecting needles in order to have a more uniform exposure of the spores to the heat. By this method the spores appear as small, dark brown globules both outside and inside the mycelia, and those contained in the mycelia are much darker in contrast to the refractile mycelia which stands out conspicuously when examined under high power.

The author also found that a saturated alcoholic solution of gentian violet and orange G. makes a differential spore stain which might be manipulated with the simplest technique, requiring only five or six minutes for the finished preparation. The formula that gave the best results is saturated alcoholic solution of gentian violet, 2.5., distilled water, 17.5; orange G. solution (No. 2), 9; chemically pure acetic acid, 1; alcohol, 95 per cent., 5.

The method used was as follows:

1. Place scrapings in small drop of water on cover slip.
2. Tease thoroughly with dissecting needles.
3. Dry over flame, being careful not to scorch.
4. Stain two minutes; pour off excess.
5. Immerse in 95 per cent. alcohol, for from one-fourth to one-half minute.
6. Immerse in distilled water, for from one-fourth to one-half minute; pour off excess.
7. Dry by heat.
8. Mount in balsam.

The spores and mycelia take the blue, and the scrapings the yellow. Normal scrapings were used repeatedly and stained by this method, but no gentian violet remained in the specimen; nothing simulated mold spores.

This stain brings out the spores very clearly when free

(7) Archiv. Dermat. and Syph., January, 1920.

in the tissue, but when they are within the mycelia, as in tinea cruris and circinata, the gentian violet will penetrate very little or not at all. The mycelia, even in these cases, will appear as pale yellow refractile strands traversing the field, and are easily recognized.

Cutaneous Lesions of *Endomyces Albicans*. The isolation of *Endomyces albicans* from the pustular lesions on the finger of a woman is reported by Tanner and Feuer.⁸ The lesion began near the finger nail of the index finger. The lesion slowly and painlessly enlarged to a diameter of from 5 to 10 millimeters and then discharged a yellow pus. At no time was the lesion painful. Within a few weeks other similar miliary abscesses formed on the same finger, always painless and rapidly discharging a purulent material. These lesions followed each other in rapid succession and in crops; at one time the distal phalanx was practically covered by a coalescing mass of the minute miliary abscesses.

A Peculiar Fungus Infection of the Skin (Scorpilze). A negress who presented lesions due to an unusual fungus was observed by Engman.⁹

The patient stated that the disease began on "an irritated spot" on the inner side of each thigh, about December, 1913, and that these spots increased in dimension until they occupied the areas at present involved.

On examination, about the upper part of thighs, sweeping out from each side of the vulva, extending farther on the right than on the left, was a sharply defined, scaly area. The condition looked exactly like that of a tinea inguinalis or that produced by *Epidermophyton inguinale*. One could not have differentiated this infection from one produced by either of the above-named organisms. Underneath each breast was a similar area, sharply defined, slightly raised, and more of a purplish inflammatory hue than that seen on the thighs. The edges of these lesions were undermined and finely papular at the border, while the furfuraceous scaly center seemed to be depressed below the surface of the normal skin.

There was some pruritus, particularly around the

(8) Archiv. Dermat. and Syph., April, 1920.

(9) Archiv. Dermat. and Syph., April, 1920.

vulva, but this was not marked. The process was very rebellious to treatment, and so was the patient. She made several short sojourns in the hospital without her condition being benefited to any marked degree.

Preparations made with potassium hydroxide in the usual manner for the examination for such organisms, disclosed a peculiar fungus. Cultures were also made. The cultures were identified by Professor Moore as belonging to the order *Moniliales* and closely resembling the well-known "*Soorpilze*" of thrush.

BENIGN NEOPLASMS.

The Histogenesis of Molluscum Contagiosum. In a paper by Wile and Kingery in this volume for 1919 were detailed a series of experiments demonstrating the etiologic agent of molluscum contagiosum. As a result of their studies, these authors were able to show that the lesions of this disease can be produced experimentally from the sterile filtrate of molluscum lesions, thereby justifying their conclusion that molluscum contagiosum is caused by a filterable virus. The technique of these experiments, as carried out on themselves and their assistants, was comparatively simple. Molluscum lesions were removed by curettement, ground up in a mortar containing a small amount of sterile saline, and the resultant mash passed through the finest Berkefeld filter under negative pressure. The filtrate thus obtained, which produced no growth on all ordinary culture media, was injected intracutaneously into human subjects, at the points of predilection for the development of this disease. After an incubation period varying from twelve days to three weeks, definite papular lesions developed at the sites of the injections. These lesions rapidly took on the clinical characteristics of molluscum contagiosum. Those examined histologically, after a developmental period of eight weeks, presented the unmistakable picture of the disease, including the so-called "molluscum bodies." The subjects of these experiments were under daily observation and histologic study was undertaken at short intervals during the entire evolution of the lesions. In this way material was obtained in-

cluding every developmental phase of the lesions, from the earliest pinpoint papule, up to the mature stage with its waxy appearance, and the central umbilication. The material thus studied offered an unusual opportunity for the investigation of lesions the histogenesis of which has been a debated question since the time of Bateman's original description of the disease (Plate IX).

It is on a critical examination of this material that the study by Kingery¹ is based.

The opposing views of many leading investigators, regarding the peculiar histologic picture presented by molluscum contagiosum, are found recorded frequently in the literature on this disease. Out of these controversies two preëminent theories have been developed, which are today used in an attempt to explain the origin of these lesions.

The first of these views to be advanced was to the effect that the lesions of this disease are related to the pilosebaceous apparatus. The other theory is that the lesions were never related either to the follicles or the sebaceous glands, but were due to a pathology concerning only the rete layer of the epidermis.

The exhaustive studies carried out by Kingery with the experimental lesions of molluscum contagiosum in the various stages of development, have demonstrated that the lesions are limited to the pilosebaceous epithelium. There is an abundance of clinical and pathologic evidence which favors the existence of the analogue of molluscum contagiosum in fowls. The absence of pilosebaceous epitheliom in the combs and the feet of the fowls and pigeons, where lesions of molluscum epitheliale often occur, justifies the conclusion that the lesions of this disease can develop independent of pilosebaceous structures. Presumptive evidence points to the identity of molluscum contagiosum in man and molluscum epitheliale in lower animals. Final proof of the development of molluscum contagiosum from the surface epithelium, therefore, must depend on the establishment of the identity of these two conditions. This identity will be proved only by the successful inoculation of molluscum contagiosum into fowls, and of molluscum epitheliale into

(1) Arch. Dermat. and Syph., August, 1920.

human subjects. Kingery is now carrying out experiments directed toward this end (Plate X).

Condylomata Acuminata. Among seven thousand seven hundred gynecologic patients at the New Haven Dispensary, Creadick² observed twenty cases of condylomata acuminata, or approximately one case in four hundred. Of these patients the youngest was 12, the oldest, 30. Of the twenty cases studied, ten gave a strongly positive Wassermann reaction. In five others with a negative Wassermann reaction the presence of gonorrheal infection was demonstrated by smears; in two the clinical history indicated a previous infection, but gonococci were not found. On the other hand, in three instances no evidence of gonorrhea or syphilis was obtained either from the history or from the clinical examination of the patient. Seven of the twenty women in this series were pregnant, and in one case the size of the tumor measured 10 by 16 by 5 cm., completely covering the external genitalia. In the opinion of the author, surgical excision offers the most efficient method of treatment.

Production of Tumors in Plants. There are many kinds of tumors in plants. These are due to a variety of causes which are principally living things, such as gall flies, plant lice, nematodes, fungi, myxomycetes and bacteria. Tumors may also be due to frost, to mechanical irritation, and, according to E. F. Smith,³ to a lack of aëration and the resulting increase in acidity of the imperfectly aërated tissues.

In the Department of Agriculture, a widely distributed harmful plant tumor has been demonstrated to be due to schizomycete. Although no bacteria are demonstrable in sections of this tumor, nevertheless they are present in it and can be isolated by the methods of the bacteriologist. By pure culture inoculations with the organism, the tumor can be reproduced at will and has been so reproduced hundreds of times. It may also be reproduced by grafting portions on suitable parts of healthy plants. This tumor possesses the power of continuous growth through several generations.

(2) Jour. Amer. Med. Ass'n, Oct. 16, 1920.

(3) Archiv. Dermat. and Syph., August, 1920.

The parasite causing this tumor produces ammonia, aldehyd and various acids, and with these substances Smith has succeeded in causing small hyperplasias in the absence of the parasite. He assumes, therefore, that it is the by-produce of the parasite liberated in the tissues which stimulates the normal cells to become tumor cells. Following out this theory, he tried in 1919 to find what results he could obtain in the absence of parasites by limiting the intake of air in various ways.

The author first experimented on the flesh of potato tubers, cutting out rectangular blocks under sterile conditions and hermetically sealing them in test tubes; the blocks rested on wet cotton. The tissues, being alive, continued to absorb water and to respire and transpire. They formed a cork layer over their cut surface and under this layer as respiration and transpiration became increasingly difficult, owing to the saturation of the air and its limited oxygen content, hyperplasias developed, rupturing to the surface. Titrations showed an increased acidity of the tissues. The author obtained the same result from whole tubers lying either in a covered pasteboard box in dry air, or exposed to the light on a table in a large open jar. The tubers pushed sprouts, but owing to lack of water these could not develop organs of respiration and transpiration (leaves) and they became much thickened and covered with numerous small hyperplasias, located under wide open stomata.

In the third series of experiments he obtained numerous small tumors from green potato stems in active growth by suddenly destroying the leafy top; that is to say the respiring and transpiring organs. This immediately stopped the upward movement of a large quantity of aerated water. Oxygen hunger and acidity developed and hyperplasias resulted. He also repeatedly obtained the same results on the stems of a variety of plants by blocking the lenticels, which are aerating organs, with Squibb's liquid petrolatum, following the petrolatum experiments of Wisniewski and of Schilling.

The most striking tumors, however, are obtained by inoculating the crown gall organism, *Bacterium tumefaciens*. Some of these are simple tumors and others

are tumors containing roots and shoots. Some also show the beginning of secondary tumors, and in the embryo-mass the invasion of tumor tissue into the embryomatous mass.

Multiple Benign Cystic Epitheliomata Associated with Xeroderma Pigmentosum. An unusual case of multiple benign cystic epithelioma coëxisting with xeroderma pigmentosum was observed by Withers and Coleman.⁴

In reviewing the extensive literature dealing with these diseases, one is impressed with its complexity, the confusion of terms and the diversity of types of lesions. There are four points of similarity between the two conditions: (1) the hereditary tendency; (2) the unknown etiology; (3) the age incidence, and (4) the appearance of lesions, chiefly on the exposed parts of the body, consisting of atrophic cutaneous changes, pigmentation and multiple carcinomatosis.

Benign cystic epithelioma (Brooke) may be defined as a circumscribed cutaneous atrophy and relatively benign carcinomatosis of unknown etiology and definite hereditary tendency, occurring in early life on the exposed portions of the skin, notably the face and hands, characterized by the formation of tiny pigmented papules, or of firm, raised, semitranslucent, pinkish, tubercular or nodular, flattened masses that show no tendency toward involution.

Brooke, in 1892, separated this condition from other adenoid skin epitheliomas and his observations have been confirmed by Fordyce, Unna, Stelwagon and others. Adamson, in 1908, attempted to point out the differences between this condition and multiple rodent ulcer, which "led to the query that has not been answered, 'as to what is the essential difference between a benign and a malignant epitheliomatous growth.' "

Xeroderma pigmentosum is, by definition, a disease of low malignancy and unknown etiology, developing in early life and tending to occur in many members of the same family. The chief characteristics are: precociously senile cutaneous changes, pigmentation and carcinomatous metamorphosis affecting exposed portions of the skin.

(4) Archiv. Dermat. and Syph., July, 1920.

Hebra and Kaposi first described the condition as a clinical entity in 1870, and Kaposi gave detailed histories and pathologic findings in 1882. Since that time, over 200 cases have been reported, more than eighty of which have been studied thoroughly with almost as many theories as to etiology and mode of origin—but these reports seem to have added little to the knowledge of the subject.

The histopathology, as reported by Kaposi, Taylor, Unna, Pollitzer, Councilman, McGrath and Stelwagon shows many associated conditions, such as sarcoma, myxoma, angioma, and granuloma—but the predominating feature is epithelioma, which may be of the prickle or of the basal cell type (Kreibach, Pernet, Halle). They are often pigmented, as in sailor's carcinoma (Unna).

Xeroderma pigmentosum has been divided into two distinct clinical types—the early malignant condition which results in death before adult life, and the delayed or late dermal atrophy associated with benign carcinomas.

The case the authors report is one of undisputed xeroderma pigmentosum, clinically, which is associated with a frank and characteristic multiple benign cystic epithelioma. It does not fall, therefore, into either the juvenile malignant or late benign class, and is unique in that it has been present from the patient's earliest recollection and has not become malignant. This patient may be in a transition stage between the two fairly distinct types.

The only treatment given this patient aside from excision of tumors for biopsy was the application of a radium plaque to fourteen of the larger lesions. This caused them to disappear in three or four weeks, leaving smooth pink scars.

Adenoma Sebaceum Associated with the Teratoma of the Kidney. The occasional reference in the literature to adenoma sebaceum associated with congenital tumors of the kidney or other abdominal viscera leads Crutchfield⁵ to report a case of adenoma sebaceum with an associated teratoma of the kidney. The patient was a woman, 27 years old, who had two normal children and a nega-

(5) *Archiv. Dermat. and Syph.*, September, 1920.

tive history. The lesions were typical in appearance and three weeks after first coming under observation, she appeared on the surgical service with a temperature of 104° F.

Death, which occurred in a short time, was followed by necropsy at which a tumor of the left kidney was found strongly adherent to the diaphragm and lumbar muscles. Many vascular adhesions passed from the capsule of the tumor in all directions. The right kidney was also about four times its normal size and of about the same consistency as the tumor mass and strongly adherent posteriorly. Microscopically, the tumor was found to consist of smooth muscle, fat and large areas of sarcoma and a diagnosis of teratoma of the kidney was made.

Etiology of Xanthoma Multiplex. A very intensive study of a case of xanthoma multiplex has been made by F. S. Burns,⁶ of Harvard University. Heretofore the investigation of the etiology of xanthoma multiplex has been directed chiefly toward the histology and the association of the diseases with hepatic disturbances and diabetes. The work of Pollitzer and Wile in 1912 showed that xanthoma tuberosum represented an irritative connective tissue hyperplasia in which the extravasation of cholesterol fatty acid ester present in excess in the blood serves as a stimulus. The finding of cholesterol led Burns to investigate the cholesterol content of the blood and also of the tissues. Blood was obtained from the patient by the usual method for a Wassermann test. In the examination of the blood for cholesterol as well as fatty acid the method of Bloor was employed. Cholesterol was found in large quantities in three of the nodules examined. The cholesterol blood content was found to be considerably increased under normal mixed diet, under low fat diet and under high fat diet. From the findings it would seem probable that xanthoma multiplex is a dermatosis and that its origin lies in increased cholesterol in the blood, the skin lesions of which are caused by its deposition in this tissue where it induces a peculiar secondary connective tissue hyperplasia.

Generalized Xanthoma. Another case of xanthoma

(6) Archiv. Dermat. and Syph., October, 1920.

which was carefully studied chemically and histologically is recorded by Queyrat and Laroche.⁶ The patient was a man, aged 48, who had a generalized eruption which consisted of plaques the color of chamois skin and variable in extent and contour, which were not very well-defined and which were only slightly elevated. They were most numerous on the nucha in the axillary spaces, over the scapular region, internal surface of the arm, the forearm, about the waist, the upper third of the internal surfaces of the thighs and in the popliteal spaces. They were also on the wrist. The plaques were symmetrically distributed and appeared to be most numerous over the zones which were exposed to friction.

Histologically, there were found occasional islands of infiltration deep in the derma and surrounded by a very slight inflammatory reaction. There was noted in particular entire absence of xantholasmic cells of the classical multinucleated type. Examination with Sudan III, however, showed marked infiltration in the derma and a few rare globules of neutral fat. The lesion was remarkable because of the infiltration and because it lacked the inflammatory reaction usually present in xanthoma tuberosum or in xanthelasma. Chemical examination showed the lipid infiltrate to be cholesterol. Examination of the blood showed only a slight increase in the cholesterol. This, however, probably is to be explained by the fact that only one examination of the blood was made. Had a series of examinations been made, the hepatic coefficient of Amberg would probably have been demonstrated. There was no demonstrable hepatic lesion. The hepatic insufficiency was probably only functional and limited to the metabolism and did not in any way concern the albumin metabolism.

Xanthoma Tuberosum in a Diabetic. A case of xanthoma tuberosum that was somewhat unusual in that the lesions were of the tuberosum type in a patient who had diabetes and in whom the lesions did not decrease in size with the disappearance of sugar from the urine is reported by Gamrat⁷.

The patient was a man of 40, who had had diabetes

(6) Bull. soc. franc. de dermat. et de syph., 1920, p. 208.

(7) Ann. de dermat. et de syph., November, 1920.

since his seventh year and who had had the xanthoma lesions since his thirty-third year. The lesions had the typical color of chamois skin and varied in size from that of the head of a pin to that of a nut. Some of the lesions were cylindrical and slightly pedunculated. Some of the lesions were isolated whereas others were grouped in large tumor masses. Under anti-diabetic treatment, the patient was rendered sugar-free but this had no influence whatsoever upon the lesions.

Gamrat agrees with Arzt in that he believes the term "xanthoma tuberosum" or in French terms "*xanthomes en tumers*" should be abandoned because the term implies the idea of a neoplasm, particularly of a benign tumor of which the characteristic element is the xanthoma cell. It is not a neoplasm but consists of an infiltration of cholesterol due to a hypercholesterolemia and the consequent infiltration in the derma of cholesterol masses leading to the production of the xanthoma lesions.

Histologically, the lesions were found to agree in every way with the histologic pictures described by other authors. The tumor mass consisted of an infiltration of a large mass of lipoid substances in which cholesterol predominated. The epidermis was somewhat thin but was intact. The base-cell layer had disappeared. Between the epidermis and the zone of infiltration there was a zone of separation but there was no evidence of inflammatory process. The cholesterol infiltration was limited entirely to the derma but extended to the lower limits of the derma almost to the subcutaneous tissue. The cholesterol was essentially intracellular and had been taken up by the cells to which the name has been given of cholesterol phagocytes. There was marked infiltration of cholesterol about the capillary vessels.

Benign Cutaneous Branchiomas. Since the malformations of branchial origin were first described by Veau about forty years ago, very little study has been given to these lesions. Darier and Halle⁸ have described an interesting case which is remarkable for its extent.

Branchiomas are divided into two classes, the benign and the malignant. The benign consist of the fibro-

(8) *Ann. de dermat. et de syph.*, January, 1920.

chondromas; of dermoid cysts or of mucous cysts. The branchial fistulas and the mixed tumors also come in this class. Under the malignant type are included those tumors which appear to have both epitheliomatous and sarcomatous characteristics and which have been called the branchiogenic carcinoma of Volkmann. Sometimes these lesions develop by malignant transformation from a branchioma which previously has appeared benign. Sometimes they seem to develop in the adult by proliferation probably of the elements of an embryonic inclusion which has thus far remained latent.

The case observed by Darier and Halle occurred in a child 11 years old. From the right ear extending downward to the internal extremity of the clavicle was a series of elevations which superficially resembled somewhat the lesions of *molluscum contagiosum*. These small tumors were arranged in a line which went directly downward from the ear and then turned sharply forward at a right angle. The lesions were either discrete or confluent. When they were examined closely there was no real resemblance to the lesion of *molluscum contagiosum*. Some of the tumors were surmounted by a very small vesicle, others had at the summit a very small lesion which suggested an epidermic pearl, some of them were surmounted by a small papillomatous lesion. When some of the lesions were punctured a very minute drop of serous fluid exuded; others, however, furnished no liquid whatsoever. The external auditory meatus was almost filled with these lesions. The child was well and strong and there was no adenopathy. She was unusually intelligent and otherwise normal in development.

Histologically the lesions were found to consist of verrucous and fistulous malformations. The fistulas, for the most part, were microscopic; some, however, were quite a little larger. No one of them extended beyond the derma. The cavities of these fistulas were the site of papillomatous vegetations developed according to the dimensions of the cavity, which they as a rule filled completely. The cavity and the vegetations were covered by a cylindrical epithelium which at the orifice of the fistula continued directly with the Malpighian epidermis. There was nothing in the appearance of

the epithelium which would enable one to make a prognosis as to the probable evolution of these lesions.

Leiomyoma. Inasmuch as leiomyomata are extremely rare the case reported by Savatard⁹ is of much interest.

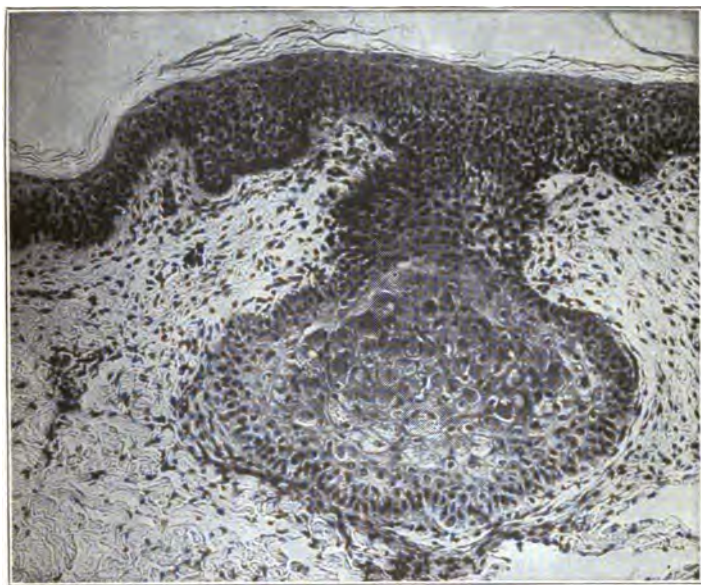
The patient was a man, 48 years old, who presented over the right malar region and on the external aspect of the right forearm numerous discrete nodules, varying in size from a pin's head to a small cherry. The color, yellowish-brown on the cheek and dull red on the arm, disappeared on pressure. The nodules were firm, though the induration varied, and were movable with the skin. Some of the larger ones were very sensitive to pressure and to changes of atmosphere and temperature. Gentle manipulation of one of the larger tumors gave the patient excruciating pain. When damp weather occurred severe paroxysms of pain were experienced in these nodules. Pain was also induced on leaving a warm room and on dressing and undressing.

The nodules were first noticed on the forearm, at the age of 18. The lesions on the cheek appeared shortly afterward. Savatard had the case under observation for five years. The nodule excised for examination has not recurred, and the photographs taken at that time present the picture of to-day. There has been apparently no visible change though the paroxysms of pain are worse, so that excision of further tumors is now indicated. Radium and x-ray were tried without effect except that no pain has been appreciated in the facial lesions since the application of radium.

Microscopically the tumor was composed entirely of smooth muscle-cells with their typically shaped nuclei. The bundles formed a branch mass, crossing each other in all directions, and extended from the pars reticularis to the subcutaneous fat. There were fine interlacing bundles of collagen fibers in the tumor proper which gradually increased in size toward the periphery of the growth, but there was no suggestion of a fibrous capsule. Sebaceous and sweat glands were not seen among the bundles nor could any nerve-filaments be detected. A hair follicle was, however, seen almost in the center, closely infested with thick strands of the new growth.

(9) Brit. Jour. Dermat. and Syph., July, 1920.

PLATE IX.



Well-developed experimental lesion of molluscum contagiosum, eight weeks old with epithelial pedicle.—Kingery, page 76.

PLATE X.



Lesions of "epithelioma contagiosum" occurring on combs
and wattles of domestic fowl.—Kingery, page 70.

Small blood-vessels showing proliferation of their muscular coat were also visible within the tumor.

The case did not present any great difficulty in diagnosis. There were the extremely slow but progressive development of the nodules in number and size; their grouping and asymmetrical distribution; their moderate size and dull red color; their firm consistence and mobility; their initial painlessness with subsequent severe paroxysmal, spontaneous and provoked pain, and their non-recurrence after removal. When, however, their character and symptoms are not typical one should not accept a definite diagnosis without a microscopic examination. Most investigators attribute the origin of the leiomyoma to the erector pili, some few to the muscular coat of the blood-vessels, and others to the erectors and the vessel coats. Although the sections showed clearly the origin from the erector pili, one could not rule out the possibility of a double origin. No investigator has found evidence of nerve implication, so that the pain has been attributed to pressure on the deeper nerves. With this explanation we must at present be satisfied, for it would appear that the deeper the growth in the corium the severer the pain. Three only of the cases have been solitary tumors, so that, as in other conditions, this fact should not negative the diagnosis.

Cutis Verticis Gyrata. An unusual case of this interesting disorder is reported by Lenormant.¹ The patient was a woman of 30, who presented nothing unusual in her personal or family history. The malformation was congenital and appeared at birth as a lesion about the size of a two-franc piece. It gradually grew and at the age of puberty had enlarged to such a degree that it no longer was possible to conceal it. The scalp at the same time became decidedly sensitive and there developed an abundant secretion, which accumulated in the depressions of the growth. When seen by the author the growth occupied the greater part of the scalp, coming down over the occiput and falling over and depressing the left ear. The appearance of the growth was markedly similar to cerebral convolutions. The coloration of the skin was approximately normal. The

(1) *Ann. de dermat. et de syph.*, 1920, p. 225.

hairs which were dark and thick were implanted only in the depths of the principal furrows and were totally absent on the heights of the convolutions. There was an absence of excoriations and inflammatory process. An attempt was made to treat the lesions by electrolysis but this attempt was finally abandoned (Plate XI).

In reviewing the literature, the author finds very few cases, but is of the opinion that it is much more common than the number of reported cases would indicate. He believes that there are a great many cases in which the lesion is so small that it passes undetected, but the extensive cases such as reported by Lenormant are certainly very rare.

Von Veress believes that the disorder is encountered only in men and that the subject is usually dark with thick and abundant hair. This does not hold true, however. The age of the patients varies from 10 to 49 years. The pre-existence of an inflammatory lesion in the scalp is cited in a number of cases. The location and extent of the lesion vary markedly. The common origin is at the back of the scalp either in the region of the vertex or the occiput. It is usually in the midline and symmetrical. Throughout the zone one finds the same characteristic thickening, the folds and laxity of the skin, and without exception they have the form of cerebral convolutions. Concerning the nature of this malformation there is a variance of opinion. Jadassohn, who was the first to describe the condition, believed it to be of the nature of a diffuse congenital elephantiasis. Unna attributed the folds to a disproportion between the dimensions of the scalp and that of the skin which had become exuberant about a sort of hyperplasia of the superficial elements, and he compared it to the folds of the nucha which are frequently observed in the obese. Pospelow regards the disorder as a congenital anomaly which manifests itself rather late under pathologic influences, possibly resulting on trophic modifications in the vestigial rudiments of the epicranial muscle of Gegenbauer. Foerner, microscopically, found no alteration in the skin and concluded that it is merely an anomalous condition comparable to the variation in the skin on the heads of various breeds of dogs.

After a review of all the reported cases, Lenormant concludes that the disorder can not be said to be a definite entity with constant anatomic alterations. There are two types of the disorder: one of inflammatory origin which is generally limited and occurs in the adult and, as a rule, follows a chronic inflammatory process of the scalp. The other is a true malformation, always congenital, usually very extensive, and covering the greater part of the scalp. This type resembles anatomically the nevi and might be called a giant nevus of the scalp.

Therapeutically, the only method of removing the lesions successfully is by surgery. Lenormant's patient was operated on successfully and the entire lesion was removed.

PRECANCEROUS DERMATOSES.

Course of Precancerous Dermatoses. The further course of two cases previously reported by Bowen of precancerous dermatoses appears in the *Archives of Dermatology and Syphilology*, January, 1920. The two cases were originally reported in the *Journal of Cutaneous Diseases* for May, 1912, and for December, 1915.

In one case, twenty-nine years have elapsed since the beginning of the cutaneous affection, and the patient has been practically free from lesions for several years, following active destructive treatment, although a tendency to recurrence asserts itself from time to time. In this case, the lesions have always remained localized in a limited territory. In another case the patient died of internal cancer in May, 1918, thirty-four years after the first appearance of the skin affection, which in his case was much more widely distributed and more varied in type.

Precancerous dermatosis, although it can not be advocated as an exact term, serves to call attention to the group of cutaneous affections which include Paget's disease of the nipple, xeroderma pigmentosum, keratosis senilis, and arsenical keratosis, in all of which carcinoma results much more frequently than in other skin affec-

tions, and all of which have many points of histologic resemblance. The cases under consideration belong in this category, at least for purposes of study, until a more scientific and exact classification can be offered.

Extra-Mammary Paget's Disease Occurring in the Axilla. It was formerly thought that Paget's disease occurred only about the nipple but now it is known that it is not uncommon elsewhere; the superficial epitheliomatosis of Paget's disease may occur on any part of the body.

A case was reported by Satani² of Kyoto, Japan. The patient was a man aged 74, who had a lesion in the right axilla with the same clinical and histologic features shown by the lesion when it occurs about the nipple. In the middle of the right axilla was found an irregular, ovoid, flat lesion 7 cm. in long diameter. The margin was sharply defined against the normal skin and was elevated and slightly rolled. The surface of the patch was covered with granulations and superficial fissures, especially in the posterior quadrant, causing this section to have much the appearance of the brain surface. Some sections of the center and the top of the wart were slightly eroded, and the entire center was of a deep red color, small portions of which were covered with thin brownish crusts.

The entire lesion was excised and studied intensively histologically.

Precancerous Lesions of the Skin of the Vulva. Examination of the vulva in 100 women of an average age of 67 years by Taussig,³ showed that all variations of vulvar atrophy may be encountered. The variation was independent either of age or the amount of atrophy in other parts of the skin or of the amount of vaginal discharge. The extreme forms of atrophy are most common in those women who have had children. Cases of extreme atrophy present at times a markedly dry and brittle skin that cracks open on merely separating the labia for inspection. In spite of the frequent lack of cleanliness, pruritus was only rarely present.

The author describes in detail the histopathology of

(2) Brit. Jour. Dermat. and Syph., April, 1920.

(3) Archiv. Dermat. and Syph., June, 1920.

simple pruritus vulvae, kraurosis vulvae, leukoplakic vulvitis and carcinoma vulvae.

The treatment of pruritus vulvae usually consists in finding the special irritative factor; namely, leukorrhea, rectal infection, toxic conditions, and removing these factors, if possible. Local applications are usually of only temporary benefit. In the more pronounced kraurosis an incision widening the vaginal outlet will at times be necessary. Leukoplakic vulvitis will improve in time under antipruritic healing lotions, but recurrent attacks always follow until more radical measures are employed. Roentgen-ray treatment is equally ineffective in the experience of most dermatologists. On the other hand, complete excision of the affected skin leads to cure in a high percentage of cases. In cancer of the vulva, Roentgen-ray and radium treatment have given satisfactory results. The experience of Taussig has been chiefly with radium.

MALIGNANT NEOPLASMS.

Malignant Degeneration in Benign Dermatoses. In reviewing the various forerunners of cancer, C. M. Williams⁴ says that there is one factor common to all, and that is irritation—usually repeated over a period of months or years. Irritation by chemicals, by actinic rays, by Roentgen rays, by germ action or by germ products, lead to epithelial hyperplasia, or it may be to atrophy and scarring, but the action seems to end there. The keratotic or sclerotic tissue, however produced, is then the starting point of a change of a different order, which we call malignant degeneration. It may be that mechanical irritation will so alter the metabolism of their component cells as to lead to the production of this hypothetical substance, but we do not know.

There are many causes which lead to keratoses and scars, and keratoses and scars are more prone to malignant degeneration than is normal skin, but the number of keratoses and of scars is so enormous and the number of epitheliomas relatively so small that the danger in each

(4) Archiv. Dermat. and Syph., August, 1920.

individual case is slight indeed. Our aim should be prophylaxis—to prevent the formation of these precancerous conditions; to watch and protect them when they appear; to remove them when exposed to injury or when they show signs of changing their character. But to recommend the removal of every scar, every nevus, every keratoma, when every person has at least one of these blemishes, or to frighten the public with tales of the menace of such growths, is not justified by the facts.

[There is need for arousing, rather than for allaying, the fear of the layman of pre-epitheliomatous hyperkeratoses, and of pigmented neoplasms. No harm is done by removal of the former and much harm may be done by neglect. The very best judgment is required to deal with the latter.—M.]

The Cancer of the Precancerous Dermatosi of Bowen. In 1912, Bowen of Boston described a dermatosis which he had observed in a few cases and which he predicted at that time would eventually end in malignancy. In 1915 the same author described a third case in which one of the areas of the keratosis had become epithelomatized.

Darier⁴ has recently observed and studied carefully a case of the precancerous dermatosis of Bowen which eventually came to autopsy.

Clinically this cancer is remarkable by its peripheral extension rather than by its extension in depth and by its tendency toward the formation of vegetation and ulceration. It gives rise to circumscribed areas of conglomerated excrescences, separated by very deep furrows which are covered by crusts and squames. Over the surface are disseminated white points which resemble the grains of millium. The growth is sufficiently rapid so that in the course of a few months, the cancer may involve the entire face. In the case under observation, persistent and rebellious hemorrhages occurred at frequent intervals. Unlike the basal-cell epithelioma, it gives rise to a regional adenopathy. The adenopathy is characterized by very small glands which are multiple and not conglomerated, and it differed in this respect from the adenopathy of the spindle-celled epithelioma.

(4) *Ann. de dermat. et de syph.*, February, 1920.

At a later stage it has a marked tendency toward the formation of metastases. These metastases take place by the way of the lymphatic vessels and eventually involve the lungs, the peritoneum and probably other viscera.

Histologically, this cancer is even more characteristic. It is made up of masses of atypical Malpighian epithelium. The cells are voluminous and frequently edematous and have nuclei which are unequal and of which a great number are of the giant type. Some are multiple or deformed and of monstrous size. These are the cells which have been described as dyskeratosis. The center of these masses of epithelium sometimes undergoes a necrotic degeneration. The stroma of the tumor is fibrous without any inflammatory reaction. The texture and the structure of the cancer is exactly the same in the skin, in the glands and in the visceral metastases. This structure is absolutely identical with that of the epidermis in the areas of dyskeratosis of the precancerous type described by Bowen, the areas in which the cancer develops directly. The only cancer with which this presents any histologic analogy which might be called striking is that of the dyskeratosis of Paget or the Paget's disease of the breast. These two dyskeratoses which are precancerous are manifestly two neoplasms which are distinct one from the other. Further research is necessary to determine whether these two cancers which develop from the two dermatoses differ sufficiently to enable one to make a distinction either clinically or histologically.

The treatment of this cancer was not at all satisfactory. Intensive radiotherapy was begun early in the disorder when the patient was first seen by Dubreuilh of Bordeaux. Later at *Hôpital St. Louis* intensive radiotherapy was likewise given without results. Darier is of the opinion that when this transformation is first observed, recourse should be had at once to surgical excision.

Malignant Angioma. Invasion of the regional lymph glands by an angioma or even by angiosarcoma is quite an unusual observation. Such a case is reported by Milian.⁵ The patient was a young woman who de-

(5) Bull. soc. franc. de dermat. et de syph., 1920, No. 7, p. 249.

veloped ulceration on the abdominal wall at the site of a congenital lymphangiectasis. The ulceration eventually resulted in the transformation of the lymphangiectasia into an angiolymphangioma of which the cells were voluminous and karyokinetic with the appearance of malignancy.

The lesion was excised and six months after the surgical operation, there was a recurrence *in situ*. The marked pigmentation suggested a melanocarcinoma or nevocarcinoma.

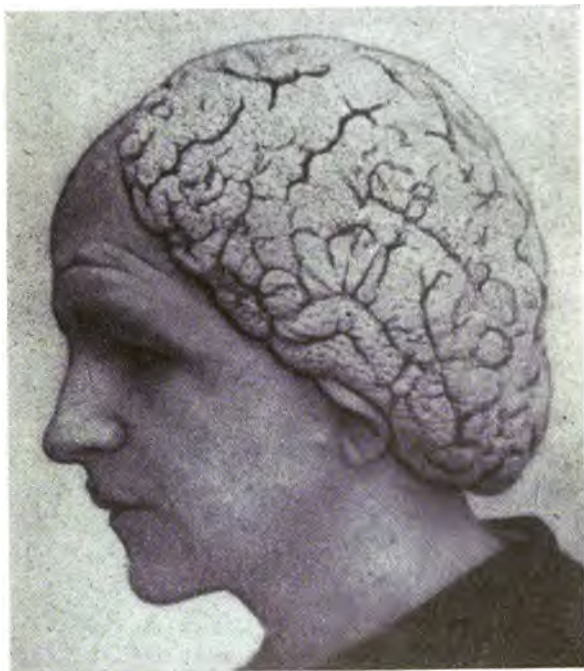
Section of one of the extirpated inguinal glands showed that it was not surrounded by any inflammatory process but when opened considerable bloody fluid exuded. Histologically, the center of the gland was a typical angioma. The angiomatous cavities were filled with blood and were bordered by endothelium which was typical and which was disseminated in the adenoid tissue. Melanotic pigment was found contained in the cells which were of the fusiform type identical with those of the angioma. In the opinion of this author the case was one of melano-angioma.

Frequency of Malignant Neoplasms Among the Natives of North Africa. The belief has become widespread that the natives of tropical and subtropical countries are much less subject to the malignant neoplasms, especially to the epitheliomas, than are the natives of the temperate regions. In spite of the reports of Brault, who reported forty-nine cases in 1916, recent publications have continued to state that the natives of North Africa are immune to cancer of the skin.

In order to determine the relative frequency of malignant tumors among the natives Montpellier and Marchand⁷ sent out questionnaires to the physicians of Algeria. The replies to the questionnaires resulted in the reporting of thirty-one new cases, making the total of cases so far reported number eighty-seven. The conclusions of the authors are that malignant tumors of the skin of the natives of North Africa are frequent; that epitheliomas are more numerous than are the sarcomas; and that the skin of the native probably undergoes malignant transformation quite as readily as that of the European.

(7) Bull. soc. franc. de dermat. et de syph., 1919, p. 317.

PLATE XI.



Cutis verticis gyrata.—Tenormant, page 81.



PLATE XII.



A.—Idiopathic hemorrhagic sarcoma showing wart-lesions on sole.



B.—Idiopathic hemorrhagic sarcoma. Later stage of condition shown in A.—Cole and Crump, page 89.

PLATE XIII.



Multiple hemorrhagic sarcoma.—Sibley, page 89.



Multiple hemorrhagic sarcoma.

Idiopathic Hemorrhagic Sarcoma (Kaposi), Complicated with Lymphatic Leukemia. The subject of idiopathic hemorrhagic sarcoma of Kaposi has already been written about from many standpoints, and to date quite a large number of cases have been reported. Cole and Crump⁸ report two interesting cases, one of which is quite unusual.

One occurred in a Russian Jew, aged 66, and the other in an Italian, aged 56. In the first case, the disease was of five or six years' duration, and in the second, of twenty years' duration (Plate XII). In Case 1, the patient developed a lymphatic leukemia in the course of his disease but throughout the course his cutaneous lesions showed the histologic characteristics of hemorrhagic sarcoma of Kaposi; i.e., the formation of new blood-vessels in the corium, perivascular infiltration with small, round cells and deposition in the tissue of blood pigment, consisting of hemosiderin. Experimentally, the authors were unable to transmit the disease to cats, white rats, guinea-pigs or to rabbits.

Multiple Hemorrhagic Sarcoma (Kaposi). A case of the so-called multiple hemorrhagic sarcoma first described by Kaposi has been studied by Sibley.⁹ The patient was a man, 72 years old, who had had the disorder about seven years. The lesions which first appeared, developed on the back of the right hand, after striking his son a blow in the face and traumatizing his hand on his son's tooth. At the point of injury, a small red spot appeared immediately afterwards and gradually enlarged. Later, large tumors developed on the feet and ankles and the lesions gradually spread upward and the face, head and neck finally developed the tumors (Plate XIII). The glands in the left groin and to a lesser extent in the right were enlarged. The other glands were not appreciably involved. The liver was enlarged and extended to about three fingers breadth below the costal arch. The spleen could not be felt nor could its area be determined. The cardiac sounds were normal.

Histologically, the layers of the epidermis were found slightly atrophic; the dermis was composed of masses

(8) *Archiv. Dermat. and Syph.*, March, 1920.

(9) *Brit. Jour. Dermat. and Syph.*, November, 1920.

of spindle shaped and round cells which appeared to be separated by a fibrous connective tissue. No mitosis was seen. There was a marked vascular dilatation and a deposition of blood pigment apart from the vessels themselves. The growth appeared to be of connective tissue origin associated with pigmentation with no true sarcomatous cells present. The author suggests that the name "multiple hemorrhagic granulo-fibroma" would be more appropriate than that of sarcoma which has previously been attached to these cases by Kaposi.

The treatment consisted of Fowler's solution internally and a few exposures to x-rays. As a result of these therapeutic measures, there was considerable improvement.

TREATMENT OF DERMATOSES.

Methylene Blue in Actinomycosis. The statement in Beeson's "Bacteriology" that one drop of a 1 per cent. methylene blue solution in 10 c.c. of broth culture kills the organism of actinomycosis led Jensen and Schery¹ to test out the therapeutic effect of methylene blue in a case of actinomycosis. It was calculated that 5 grains of the drug would keep the blood serum saturated with the methylene blue; therefore, this dosage was given the patient several times a day. Attempts were made to determine the concentration of the methylene blue in the patient's serum, but these both were all negative. During the course of the treatment, methylene blue in 3 per cent. solution was injected locally. Radiotherapy was likewise used and the patient made an excellent recovery. It is, therefore, impossible to state what value, if any, methylene blue has in actinomycosis, because we know that radiotherapy is of great value.

Treatment of Lupus Vulgaris with Liquid Acid Nitrate of Mercury. H. G. Adamson² has revived a method first mentioned in the *Medical Times and Gazette* in 1885.

"A solution of the nitrate of mercury in strong nitric

(1) Jour. Amer. Med. Ass'n, Nov. 27, 1920.

(2) Brit. Med. Jour., July 24, 1920.

acid is in very common use at the Hospital for Cutaneous Diseases, and constitutes a very convenient form of caustic. Its formula is:

R	
Hydrargyri	ʒi
Acidi nitrici (sp. gr. 1.50).....	ʒiii
Solve.	

The solution produced is a clear, colorless fluid."

Adamson's experience with the treatment of lupus with acid nitrate of mercury covers only a period of some nine months, but the results obtained have been so successful that one wonders why this already known remedy should have remained neglected.

The cases which have been treated by this method in the skin department at St. Bartholomew's Hospital may be arranged in four classes:

1. Single patches of non-ulcerated lupus of the size of a shilling (twenty-five cent piece) to that of half a crown (half dollar), and which have received no previous treatment.

2. Old cases of lupus which have been treated by other methods, but in which lupus nodules still remain in the scars.

3. Ulcerated lupus, often of large extent and with much surrounding inflammatory infiltration.

4. The common type of lupus of the nose, involving frequently also the nasal septum, the palate, the upper lip, the cheek, and sometimes the lachrymal sac and skin over and around, a type very difficult to deal with by Finsen light or by scraping.

The liquid acid nitrate of mercury is applied by means of a small swab of wool tightly twisted round the ends of a finely pointed pair of forceps. It is painted on to the affected areas freely and with firm pressure for from one to two minutes, care being exercised to limit the application exactly to the lupus patches, to isolated nodules, or to ulcerated surfaces. In the case of isolated nodules or non-ulcerated lupus patches the effect of the application is after a minute or so to change the semi-translucent reddish-brown "apple jelly" lupus tissue, so that it takes a dry yellowish-white opaque ap-

pearance. No dressing is applied and the patient is seen again in a week. The yellowish-white opaque appearance has then given place to a thin brownish crust, which falls in a few days and leaves the affected area sometimes completely healed, sometimes as a shallow ulcer which heals in a few days. In many instances a single application has been sufficient to replace the lupus by a smooth healthy scar without any remaining lupus nodules. In other cases with isolated nodules repeat the application one or more times. The application is only slightly painful at the time, but is followed by more severe pain for several hours.

In the case of ulcerated lupus, after removing all crusts, the solution is freely painted on to the ulcerated surface. This causes considerable pain, but if a not too large area be done at one sitting it is easily borne by most patients. The after-effect upon ulcerated surfaces is rather different from that upon non-ulcerated lupus. The surface of the ulcer becomes dry yellowish-white, but in a few days much serous exudation gives rise to a thick heaping up of crust. At the end of a week the crusts are picked off, or bathed off, and there is then an ulceration with purulent surface, and a margin of pink healthy epidermis which heals in the course of a week or so. The number of applications required in ulcerated lupus depends upon the extent of the disease and the depth of the inflammatory infiltration which often accompanies these ulcerations.

In those cases in which the nose is involved the treatment by Finsen light or scraping is rendered difficult owing to the deep involvement of tissues other than the skin. The disease, which usually starts in the mucous membrane of the anterior part of the septum and spreads thence through the whole thickness of the nose to appear as nodules in the skin of the nose, sometimes also perforates or destroys the cartilaginous septum, spreads upward to involve the lachrymal sac, downward to the upper lid, backward to the hard and soft palates, and along the lymphatics to appear upon the skin of the cheek midway between the nose and the ear. But even in these difficult cases where much of the disease would seem to be out of the reach of a local caustic application,

the liquid acid nitrate of mercury has produced far more rapid improvement than any previously adopted method of treatment. A lachrymal abscess may be swabbed with the solution. The solution may be carefully painted on to lesions in the nose or on mucous membranes, and all nodules or ulcerations on the skin surface similarly dealt with.

In extensive cases all this may be done at one "sitting" under a general anesthetic; but it can also be carried out gradually without any anesthetic by applying the acid little by little to different parts at different visits. No complete cure can as yet be claimed in an extensive case of lupus. The period of employment of this remedy has not yet been sufficiently long. But the good results already obtained seem to justify a more general use of the acid nitrate of mercury in the treatment of lupus.

Treatment of Buccal Leukoplasmia with Carbon Dioxide Snow. The results obtained by Ravaut and Gallerand³ led them to report this method of treatment which, in their opinion, is more satisfactory than any other they have used.

[The use of carbon dioxide snow has been much neglected in France. Only recently have they begun to take it up, as the article indicates. The snow has been used in leukoplasmia for years in America.—M.]

Treatment of Erysipelas with Brilliant Green. To the already very long list of drugs used as local applications in erysipelas, brilliant green is now added by J. E. Adams.⁴ The method consists in painting the affected area with a 5 per cent. aqueous solution once a day in mild cases and twice a day in severe cases. No dressing has been applied by Adams except a piece of lint on some parts of the body to prevent staining of the bed-clothes. When the eruption has subsided, the discoloration can be removed in three or four days by vigorous washing, preferably with ether soap.

Treatment of Alopecia Areata with Quartz Lamps. A series of fifty consecutive cases of alopecia areata from private and dispensary practice has been treated

(3) *Ann. de dermat. et de syph.*, March, 1920.

(4) *Brit. Med. Jour.*, Nov. 20, 1920.

by Howard Fox.⁵ Of these cases, thirty-three were males and seventeen females. They varied in age from 4 to 50 years but the majority were adults. Six of the cases occurred in children of 10 years or less. All were cases of alopecia areata of the scalp. In one patient, the alopecia was absolutely complete while in five others, it was nearly so. One patient, presented, in addition to a number of patches on the vertex, a border of alopecia extending around the scalp, of the juvenile type. Of the other cases, fourteen suffered from single and twenty-nine from multiple areas of baldness. Of the fifty patients treated, twenty-seven were completely cured and a thick growth of hair entirely covered all the bald areas. There were twelve cases classed as improved and the patches became covered by downy hair when the patients discontinued treatment. Of the remaining eleven cases, which were unimproved, the majority had not been treated longer than three weeks. Four cases were still under treatment at the time of writing.

The patients were treated, as a rule, at intervals of one week or more, according to convenience. It was aimed to produce an erythema that would remain for at least one week. At times the erythema was accompanied by vesicles or bullae. A standard distance from lamp to skin was adopted but the time was increased later as the strength of the lamp decreased due to etching of the burner and deposit of lime and iron from the circulating water.

The author is convinced that this method of treating alopecia areata is more satisfactory than any other method he has yet tried.

Treatment of Sarcoid of Boeck-Darier. In 1913 and 1914 Ravaut published several observations showing the frequency of positive reactions of the Bordet-Wassermann and the easy re-activation of this reaction in patients suffering from tuberculides and also that the administration of arsphenamine frequently gave excellent therapeutic results. This author contented himself with reporting these observations and made no suggestions as to the etiologic value of these observations. Later, Pautrier reopened the discussion, because of the fact

(5) Med. Record, Nov. 27, 1920.

that he had observed cutaneous sarcoids co-existing with typical syphlides. Inasmuch as there was complete healing of these lesions after arsphenamine injections, Pautrier was of the opinion that the cutaneous sarcoid was of syphilitic origin.

Civatte and Vigne⁶ have recently studied carefully a case of cutaneous sarcoid of the Boeck-Darier type. The patient was a young woman, without any antecedents suggesting tuberculosis or syphilis. The preceding Wassermann tests were negative. She was given arsphenamine intravenously and the lesions promptly disappeared clinically, but histologically they were not healed and persisted.

Their studies lead Civatte and Vigne to conclude that the cutaneous sarcoid of the Boeck-Darier type constitutes a definite clinical entity. They were not able to take these factors and give the etiology. The lesions resemble tuberculides more than any other lesion but there is nothing whatsoever at the present time to indicate that they may not typify syphilis. The fact that they frequently yield to arsphenamine therapy does not prove their syphilitic origin. The results of arsphenamine therapy are irregular and inconstant and are not to be depended upon.

Intensive Treatment of Psoriasis. While with the American Expeditionary Forces, W. H. Mook of St. Louis observed the treatment of psoriasis by means of 10 per cent. chrysarobin ointment containing 2 per cent. phenol. Mook⁷ describes this method in detail and is convinced that it is of great value in treatment of psoriasis of the generalized type. Three ointments are necessary and the patient must be hospitalized and visited daily. An ointment of salicylic acid and ammoniated mercury, 5 per cent. each, in petrolatum is rubbed into the scalp once daily. For protection modified Lassar's paste is applied to the normal skin about the psoriatic patches and also is used after the development of the chrysarobin dermatitis. After applying Lassar's paste to the normal skin between the patches, a 2 per cent. phenol and 10 per cent. chrysarobin ointment

(6) *Ann. de dermat. et de syph.*, May, 1920.

(7) *Archiv. Dermat. and Syph.*, October, 1920.

is applied to the involved areas. The patient should be warned in regard to the danger of conjunctivitis from the chrysarobin and be given directions to prevent its occurrence. After application of the two ointments corn starch or talcum powder is dusted freely over the entire body and the patient is advised to abstain as long as possible from walking or exercising, although it is not necessary to remain in bed. Bandaging the extremities is unnecessary and causes discomfort. A large arm chair in the room will be found to be comfortable. Applications are made once daily until the chrysarobin dermatitis begins to develop, after which they must be discontinued. A marked chrysarobin dermatitis usually appears in from three to six days, but it is less marked than when the chrysarobin lotion is used.

[We have recently seen a patient who attempted to carry out this treatment by himself. After the disappearance of the psoriatic lesions the marked chrysarobin dermatitis continued and an acute, almost universal attack of psoriasis followed. From the statements of the patient it appears that at the time of beginning the treatment he was undergoing an exacerbation. The lesions cleared, however, and it was not until the chrysarobin dermatitis became very severe and generalized that the psoriasis lesions reappeared.—M.]

Hydrargyris from Ammoniated Mercury Ointment in the Treatment of Psoriasis. Chamot states that from 30 to 40 grains of ammoniated mercury taken internally will produce dangerous symptoms. A case observed by Bechet⁸ is interesting because of the fact that the application of an ointment containing approximately six grains to the ounce, and applied twice daily, using about two ounces a day, produced very severe ptialism in a patient who had psoriasis.

Adrenalin in Erythromelalgia. The use of adrenalin in erythromelalgia probably has been made for the first time by Chatellier.⁹ The patient was a young woman, 23 years of age, who suffered from very severe crises. Various forms of treatment were tried without success. Finally it occurred to Chatellier to make use of adren-

(8) *Archiv. Dermat. and Syph.*, June, 1920.

(9) *Ann. de dermat. et de syph.*, May, 1920.

alin. Subcutaneous injection of adrenalin was followed immediately by relief and eventually by permanent cure.

Venipuncture in Cutaneous Therapy. Blood-letting is probably the oldest therapeutic measure known and it was one of the first methods of treatment used in the management of skin diseases. Hunt in discussion of the methods of treatment of skin diseases states: "No other method of treatment has yet been matured." In those early days Hunt bled to faintness, a practice often followed by great improvement in cutaneous irritation and speedy relief from pruritus. However, he used the method only to a limited extent and did not consider the results encouraging, although the method had been strongly recommended by Sir William Jenner and Bazin.

The use of autogenous serum was revived by Gottheil and Sattenstein, and later Howard Fox treated twenty-eight cases of psoriasis with autogenous serum, followed by chrysarobin ointment, with excellent results.

In the past few years Kingsbury and Bechet¹ have been bleeding various dermatoses. The authors practice venipuncture extensively in psoriasis, dermatitis herpetiformis and urticaria, and have used it in a few cases of erythema multiforme and dermatitis medicamentosa. They advise against the use of the method in asthenic, depleted, or chlorotic patients. The amount of blood withdrawn varied from 100 to 300 c.c., depending on the asthenic condition of the patient. The blood was usually withdrawn at weekly intervals. No attempt is made to explain scientifically the value of the method. In psoriasis, blood-letting seems to be of value in the acute cases with marked congestion around the lesions. Such patients were invariably benefited. In erythema multiforme it is of decided value. In dermatitis herpetiformis the method invariably improves the condition of the eruption but leaves the subjective symptoms. The most gratifying results, however, were obtained in urticaria, particularly in that type of the disease with large wheals and associated angioneurotic edema, with intense pruritus. Kingsbury, while in service in France, treated a number of cases of urticarial

(1) Jour. Amer. Med. Ass'n, Oct. 2, 1920.

eruptions following the injection of antitetanus serum in wounded soldiers with excellent results.

[Since the work of Gottheil, Sattenstein, Fox and others, we have treated a great many cases of psoriasis, and a considerable number of cases of dermatitis herpetiformis, with autogenous serum. All cases of psoriasis are benefitted, but it appears that the first series of injections gives better results than subsequent series. In fact, one rarely fails to get complete clearing of the patient after the first series of injections. In most cases of dermatitis herpetiformis the intense pruritus ceases, and the vesication is greatly diminished or disappears temporarily, and the periods of remission are greatly lengthened.—M.]

Disseminated Granuloma Annulare Treated with Tuberculin. A case of granuloma annulare in a child of 14 years was treated by Hudelo, Civatte and Rabut² by the intradermic injection of tuberculin in progressively increasing doses. The treatment was begun on October 14 and by November 20 the lesions had completely disappeared. The therapeutic result is looked upon by the authors as further evidence of the relationship of granuloma annulare to sarcoids and certain other tuberculides.

Treatment of Larva Migrans or Creeping Eruption. Most of the methods of treatment for larva migrans or creeping eruption are painful and uncertain in results. Kime³ suggests a simple, efficient, quickly and easily applied remedy consisting of salicylic acid from 10 to 20 grains to the ounce of collodion. This should be painted well over the eruption, especially at the points of migration, twice daily and the eruption will soon disappear. The collodion obstructs the migration and the salicylic acid destroys the larva.

Digestive Anti-Anaphylaxis in Treatment of Urticaria. It is well recognized that certain cases of urticaria are due to sensitization to food protein. An attempt has been made by Pagniez and Vallery-Radot⁴ to desensitize these patients by giving them a very small quantity of the protein which is implicated in the pro-

(2) Bull. soc. franc. de dermat. et de syph., 1920, p. 12.

(3) Jour. Amer. Med. Ass'n., Feb. 21, 1920.

(4) Ann. de dermat. et de syph., October, 1920.

duction of the urticaria about one hour before each meal. They found that this procedure enabled the patient to ingest the particular protein to which he was sensitized without developing an attack of urticaria.

Continuing their observations, the authors found that giving 50 cg. of peptone one hour before each meal enabled the patients to continue the ingestion of the protein without further attacks. The authors give in detail the facts concerning a number of cases which seem to show that the method of treatment is of considerable value.

Treatment of Pernio with the Uviol Lamp. In a series of 100 cases of pernio Müller⁵ has found the uviol lamp of greater value than any other method of treatment he has yet tried. The uviol lamp is a forerunner of the quartz lamp and differs from the latter in that the uviol glass acts in a way as a filter, somewhat resembling that of the filter used with the Roentgen ray. Filtering out the irritating rays by the use of the uviol lamp permits of longer exposure to the rays, and of much greater therapeutic efficiency.

Modification of Harrison's Treatment for Ringworm of the Nail. Harrison advises scraping the nail, and then applying on lint for fifteen minutes one part of potassium iodid in eight parts of a 50 per cent. solution of potassium hydroxide. Afterward, mercuric chloride, 1 per cent. in equal amounts of alcohol and water, is kept in contact for twenty-four hours.

A. L. Glaze⁶ has modified this technique so that its disadvantages are obviated. By Glaze's method, the remedy is confined to the plate and matrix, and the horny tissue is easily removed.

If the finger nails are to be treated, the patient grasps a towel-covered book so that the parts are supported in a horizontal plane. Petrolatum is generously banked about the nails in such fashion that each forms the bottom of a little lake. These are half filled with Harrison's potassium solution, and the softened plate is scraped through the fluid.

The after-treatment with mercuric chloride sometimes

(5) Dermat. Zeitschr., February, 1920.

(6) Jour. Amer. Med. Ass'n., Sept. 11, 1920.

causes severe dermatitis. In its place, a saturated solution in water of sodium thiosulphate (hyposulphite) should be used. It is applied on absorbent cotton, under a rubber finger-stall, six hours or longer daily, for three days.

Treatment of Ringworm of the Nails. Two cases of onychomycosis were treated by Craik⁷ by applications of a lotion of 1 dram of salicylic acid in $\frac{1}{2}$ oz. methylated spirit. This solution was painted on after scraping every night, and without scraping every morning, and was used for three months or longer. Both patients have been cured for twelve months.

RADIOTHERAPY IN DERMATOSES.

Physics of the Roentgen Ray. An excellent discussion of the physics of x -rays and the method by which the dosage can be determined is given by Shearer.⁸

The electrical conditions of operation fix absolutely the radiation delivered per second by a given target; hence adequate control of these conditions will enable complete duplication of radiation both in amount and quality. The two factors to be noted are: (a) Spark gap or tube voltage; (b) current in miliamperes. Of these, the former is by far the more important. The amount received by a given layer of tissue when the tube is operated for a definite time under prescribed electric conditions depends on two things: (a) The distance from the target; (b) the nature and thickness of all material through which the rays have passed before reaching the tissue treated. The reaction to Roentgen rays by living tissue is due to rays absorbed but there is no evidence at present that the biologic effect depends on the particular wave lengths absorbed. The biologic effect doubtless depends not only on the total amount absorbed, but to some extent on the rate of absorption; in other words, on the frequency of treatment as well as on the quantity of radiation. Layers of tissue near the surface of entrance always receive and absorb more radiation than the deeper layers. The inequality of ab-

(7) Brit. Med. Jour., Feb. 7, 1920.

(8) Archiv. Dermat. and Syph., June, 1920.

sorption between deep and surface layers due to decrease of intensity with distance is reduced by increasing the distance of the tube from the skin. The inequality of dose between different layers is reduced by the use of filters. This inequality is also reduced by operating at a moderately high voltage.

Assuming that one desires to limit the effect as far as possible to a thin surface layer, these facts would indicate a tube fairly close to the skin, operating at rather low gap and without filter. On the other hand, if one wishes to minimize the skin effect and secure more absorption in the deeper layers, the reverse would be true within reasonable limits; namely, greater target skin distance, higher spark gap and filtration.

Measurement of the surface radiation can be accomplished only by using some device to absorb all or part of the rays and show some observable change due to this absorption. Only a few such absorbers have been found, such as a photographic film or a layer of platino-barium cyanide crystals. Unfortunately, these indicators are troublesome for two chief reasons: (1) they absorb a different percentage of the total radiation for different voltages; (2) successive equal amounts of radiation absorbed do not give equal changes in the indicator. There is, therefore, no definite connection between their reading and the amount of radiation absorbed by the various layers.

The author believes that the physical side of this work and the apparatus should be developed to such a point that the therapist need have no doubt of his dosage and will not have to depend on any of the pastille or photographic methods of measurement. This will require coöperation and training, but would be amply rewarded by the increased usefulness and more extended application of this therapeutic agent.

Estimation of Saturation in Radiotherapy. An ingenious method whereby the amount of radiotherapy necessary to keep the tissues saturated has been devised by Kingery.⁹ Proceeding on the basis of the hypothesis that the decreasing residual effects of the Roentgen rays follow a logarithmic curve, a series of experiments were

(9). *Archiv. Dermat. and Syph.*, April, 1920.

undertaken. Assuming that these residual effects decrease according to such a law, the velocity of this decrease, at any given time, should vary directly with the concentration of the irradiation effect in the tissue at that time. In other words, the greater the amount of ray absorbed, the higher the initial velocity of loss. At such time, therefore, as this concentration has decreased by one-half, the corresponding time rate of loss shall have decreased by a similar amount, and so on, until the residual effect has become negligible. This condition

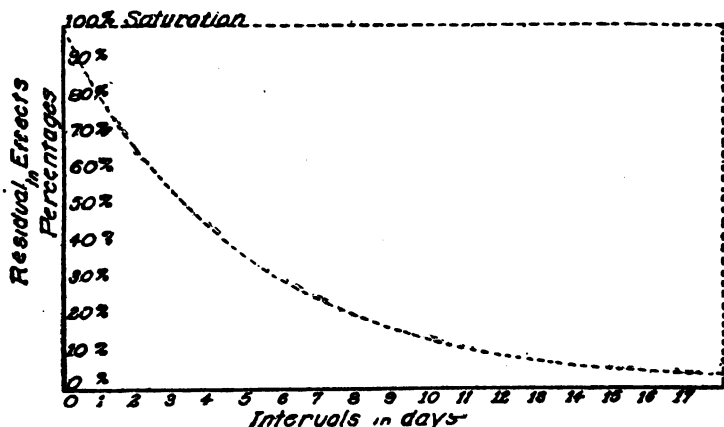


Fig. 2. Curve of residual effect. Showing gradual decrease in tissue effects, following one full dose of Roentgen ray; also sequence of events occurring in the method of "massive dosage."

we know from experience, is reached somewhere in the neighborhood of the fourteenth day.

The first experiment consisted in repeating full doses every fourteen days, the longer and therefore safer interval. The trials were without unfavorable complications. The next experiment consisted in determining after what interval of time 75 per cent. of the full dose might be repeated. Using this constant dosage and gradually decreasing the time interval, it was found that 75 per cent. of the full dose might be repeated after seven day intervals. In a similar manner was established the three and a half day interval for repetition of 50 per cent. of the dose. From these results, the curve of residual effect (Fig. 2) was constructed.

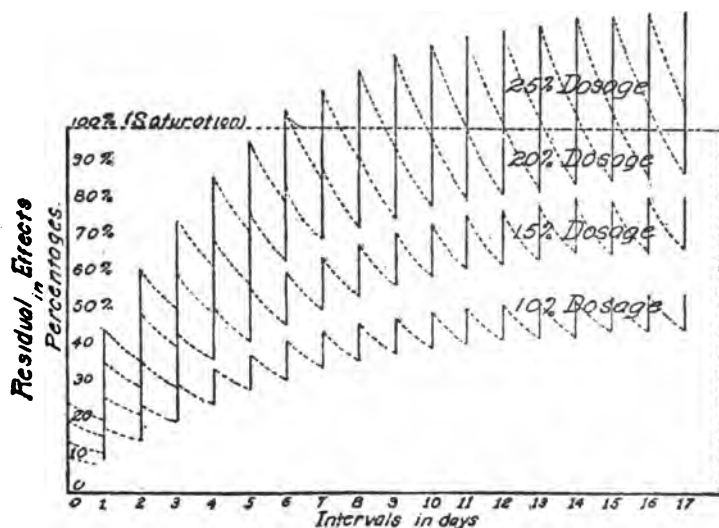


Fig. 3. Showing sequence of events occurring in method of "fractional dosage." Note gradual rise in value due to cumulative effect of small doses at daily intervals.

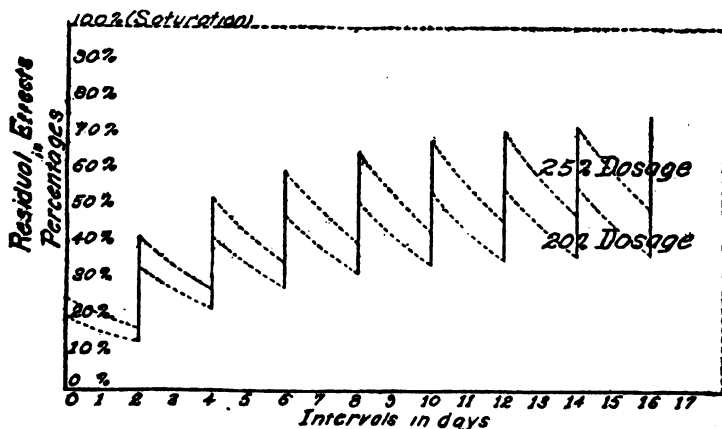


Fig. 4. Similar to Figure 3, with the exception that doses were given on alternate days.

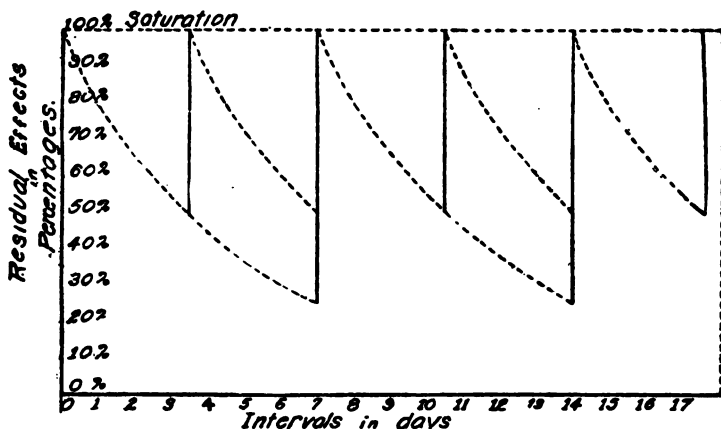


Fig. 5. Sequence of events in methods of present study. Result of administration of 50 per cent. of full dose every three and a half days, and of 75 per cent. of full dose, every seven days, following initial full dose, of 100 per cent.

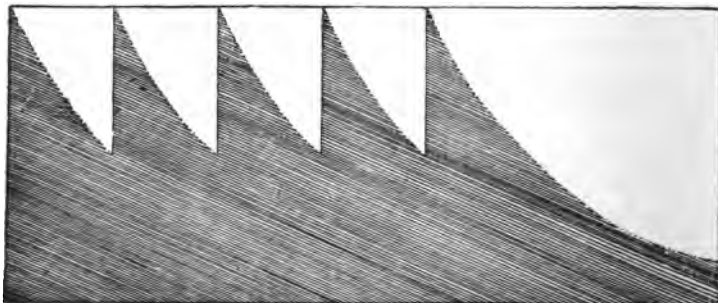


Fig. 6. This represents graphically the average treatment of five cases of moderately advanced basal cell epithelioma. These cases were chosen from a series, as it so happened that they returned at regular intervals for treatment. Each received an initial maximum dose, and four subsequent doses, each 50 per cent. of the original full dose. The intervals are each three and a half days. The shaded portion shows the residual tissue effect. This is practically always above 50 per cent. and is, at short intervals, returned to maximum. A comparison of the shaded area with that accompanying one large dose and its loss, or that of the fractional method with its initial period of incomplete saturation, readily emphasizes the differences in effects maintained.

Figure 2 represents the sequence of events under the conditions of large doses at long intervals, that is, the massive dose method. The curve represents the gradual decrease in residual irradiation effects. On the verticals is read the residual effect of the dose given in percentages of the hypothetical maximum or erythema dose, and represented by 100 per cent. Horizontally is indicated the elapsed time in days. It may be seen that at the expiration of three and one-half days, the residual effect has been reduced to 50 per cent. After a lapse of a second period, a total of seven days, it has been reduced to 25 per cent., or just half the amount present at the beginning of this second three and one half day period. Similarly in ten and one half days it has fallen to 12.5 per cent. and at fourteen days to approximately 6.25 per cent. Thus, it is seen that as the concentration of the irradiation effects decrease, their rate of loss is lessened in direct proportion, and the curve might be continued indefinitely. The residual effect soon reaches a value which is negligible, however, so that it is safe to repeat a full dose after a period of two or three weeks. Particularly interesting is the initial rapid decline of the curve. The period of time, therefore, during which the tissues anywhere nearly maintain the maximum and presumably optimum effect is relatively short. According to our present conception, small amounts of ray stimulate cellular metabolism and division, larger amounts inhibit these processes, while the maximum dose tolerated is necessary to result in the lethal cell effect. The importance of the latter is well exemplified in the treatment of new growths. At present it is impossible to determine the transition from the destructive to the inhibitory, and thence to the stimulating phases. These are peculiarities of the individual cells and cell types, rather than of the tissue mass as a whole. Yet it would seem from the descent of the above curve that the stage of destructive effect is relatively brief, and that it soon reaches the phase of stimulation where the influence is directly opposed to the effect desired.

The advantages of the method as set forth by Kingery are as follows:

Accuracy with which desired irradiation effects may be obtained and continued.

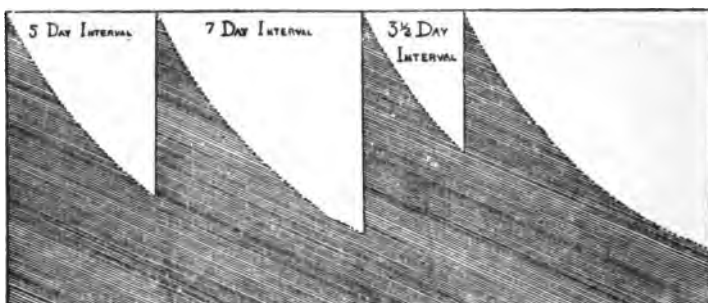


Fig. 7. This figure illustrates the flexibility of the method. The patient required continued intensive therapy, yet could not return at regular intervals. The initial dose was the ordinary full dose, 100 per cent. The patient returned five days later. The residual effect at this time is approximately 37 per cent. The patient received the amount required to return the tissue to saturation. The next interval was seven days, and again the proper percentage of the original dose was given. The last interval was three and a half days when, due to clinical improvement, the patient was saturated for the last time. Thus, after each interval, it was possible to estimate the residual effect and give the patient the benefit of the maximum dosage, with safety. Likewise the treatment, at any time, might have been continued in another more accessible laboratory.

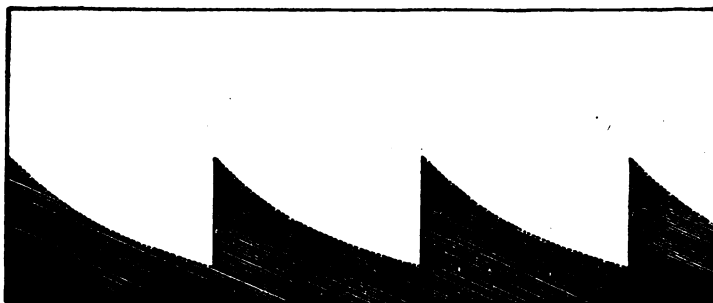


Fig. 8. In this figure is represented the treatment of a series of cases, in which maximum effects were not required. The initial dose was one-half the full dose, and at weekly intervals the patients returned to have the effects reinforced; in other words, continued mild stimulation.

Avoidance of stages of incomplete saturation, perhaps of questionable influence by properly measured doses at proper intervals.

Ability to duplicate effects accurately after various time intervals, even by different operators.

Constant protection of patients from the results of improper time and dose relations (Figs. 3 to 8).

Radiotherapy Combined with Excision for Keloids. Keloids or hypertrophied scars are difficult to treat and require much patience on the part of both physician and patient. So far as is known, the Roentgen ray and radium are the only two agents which will arrest the disease or cause it to disappear. If these agents are used early when the scar begins to hypertrophy there will probably be no need of combining excision with the radiotherapeutic effect. It is because of the frequent neglect of hypertrophied or growing scars that it is necessary to call attention to these methods of treatment. Pfahler¹ urges the early treatment by radiotherapy of all hypertrophied scars which show a tendency towards becoming keloids.

The Roentgen rays have long been used in treatment of keloids not only by Pfahler but by many others. MacKee has been especially prominent in calling attention to the value of this method of treatment. The early work was done, as most radiotherapy was done early, by fractional and indefinite doses. Even with this indefinite technique some brilliant results have been obtained. Generally, the aim should be to produce a progressive atrophy without erythema or destructive effect on the skin or overlying epithelium. The technique will vary considerably with the thickness or size of the keloid, especially in the cases in which the Roentgen rays alone are used. The thicker and older keloids will require more filtration and correspondingly longer treatment. In recent cases of hypertrophied scars, in which the scar tissue is still quite young, considerably less treatment and less filtration is necessary. In these mild types one can use to advantage 5 milliamperes of current, 2 millimeters of filter, with a focal distance of 8 inches, a parallel spark of 9 inches, for a period of 2 minutes. This will give approximately eight-tenths of an erythema dose and will be within safety limits. This treatment can be repeated in three or four weeks. It must be borne in mind that the factors given will vary in value considerably according to the instrument used, and one must familiarize

(1) Archiv. Dermat. and Syph., August, 1920.

himself with the value of each particular instrument. In the thicker and older cases of keloid which one is trying to eliminate by the Roentgen-ray treatment alone, it is desirable, when possible, to obtain a cross-firing effect. When this is possible, the area to be affected is divided into two or more portals of entry, and the rays so directed through these various fields that the deeper portions of the rays will cross in the deepest portion of the tumor. In these cases it is desirable to use the following technique: 5 milliamperes of current with 6 millimeters of filter, a focal distance of 8 inches, and a parallel spark of 9 inches for a period of eight minutes.

Radium will give very similar results if used in corresponding doses; that is, in the treatment of keloids one can produce results almost identical with those obtained from the use of the Roentgen rays. Plaques or capsules may be used. One should learn the value of the particular specimen that is being used, and it should be used long enough to produce an erythema dose, with a filtration equal to approximately 0.5 mm. of silver. This will eliminate about 98 per cent. of the *beta* rays. The duration of treatment will vary according to the size of the specimen used and the size of the keloid which is to be treated. In order to use the radium skilfully, the value of the specimen over a given area with the filtration above mentioned at a given distance should be known. From this the necessary distance and area can be calculated according to well-known methods. A 50 mg. capsule in 0.5 mm. of silver and 1 mm. of rubber in direct contact will produce an erythema dose in one hour.

The important point brought out by Pfahler in his paper is the combined use of excision and radiotherapy. MacKee was one of the first to practice this method of treatment but he advised the excision and later treatment with radiotherapy. Pfahler, however, reverses this and applies the Roentgen rays to the keloid area preceding the operation, preferably a few days to two weeks before, and of such a dose as one would give if the rays were to be depended on to remove the keloid. The keloid or hypertrophied scar is then carefully excised. This can be done best when there is sufficient loose tissue or

skin around about to close the wound without too much stretching and the surgeon should excise as nearly as possible to the outline of the keloid and not attempt to excise wide of the area. Surgeons, unfortunately sometimes make a wide incision as they would when removing a malignant growth. This extensive excision only increases the area of scar tissue, for even though the keloid is excised, there will always be a scar. The advantage of excision and combined pre-operative and post-operative roentgenotherapy consists in the reduction of the scar to the level of the skin and in many instances of a decrease in the total area of the scar. The author advises a full dose of Roentgen rays within a week or ten days after the excision of the scar. The patient is then seen weekly, and if there is any tendency toward recurrence, more treatment must be given. Three or four applications of the rays should be given to guard more certainly against a recurrence of the keloid.

Radiotherapy of Oriental Sore. After treating with radiotherapy 130 cases in which there occurred 207 sores Ormerod² concludes that x-ray therapy is the most valuable method of treatment he has yet used. The rays act directly on the causative organism and are able to penetrate unbroken skin or masses of diseased tissue, thereby being efficient in ulcerated and non-ulcerated sores alike. Cases can be treated as out-patients and the patients very often can continue their occupation. There is no risk of constitutional disturbance and the danger of dermatitis or necrosis is absent. The treatment is short, painless and easy to administer. Sores in awkward positions, such as the inner canthus of the eye, lip, and alae nasi can be very readily dealt with. The scars left after healing are supple and of such color after about six months as to be barely noticeable.

Treatment of Radio-Epitheliomas by Radium. An excellent result was obtained by Degrais³ from the use of radium in a case of hyperkeratoses and epitheliomata on the dorsal surface of the hand of a physician who had been working for years in radiotherapy. Under radium

(2) *Lancet*, Oct. 30, 1920.

(3) *Bull. soc. franc. de dermat. et de syph.*, 1920, p. 2.

treatment the cicatrization of the epitheliomatous lesion, along with complete disappearance of the violent pain which had existed, led to the belief on the part of Degrais that amputation might be avoided by the use of radium.

VENEREAL DISEASES.

GONORRHEA.

Method of Cultivating the Gonococcus. A new culture method for the gonococcus, the chief feature of which is the maintenance of low oxygen tension is described by E. O. Swartz and D. M. Davis.⁴

The medium is a 2 per cent. beef or veal infusion agar, prepared in the ordinary manner, which is brought to a reaction of pH 7.6 with phenolsulphonephthalein as an indicator. After autoclaving, the reaction comes to about pH 7.4. Sterile ascitic, pleuritic or hydrocele fluid is added to the melted agar in the proportion of one part of fluid to two parts of agar. The tubes are then corked with sterile rubber stoppers and slanted. This corking prevents evaporation, and allows the medium to be kept in the incubator, which detects any contamination and keeps the medium warm for incubation at any time. The rubber stopper has the further advantage that it prevents contamination much more surely than the ordinary cotton stopper.

The inoculation is made as plentifully as possible. It is important to have the medium at body temperature when inoculation is made, to keep it so thereafter, and to prevent cooling of the material before inoculation. Immediately after inoculation, the tube, held horizontally, is turned so that the agar slant is uppermost. Held by the butt, it is then passed longitudinally through the Bunsen flame about three times and quickly corked. Experiments with suitable apparatus show that this procedure heats the air in the tube sufficiently to cause the pressure within to be lowered from 70 to 100 mm. of mercury (about 10 per cent. of at-

(4) Jour. Amer. Med. Ass'n., Oct. 23, 1920.

mospheric pressure) when the tube is again cooled to 37.5 C. Yet the medium is not coagulated nor are the gonococci harmed. By following this simple technique one obtains with perfect regularity visible colonies in from twelve to fifteen hours, and profuse growths in twenty-four hours. The viability of the gonococcus on this medium is about seven days. Pure cultures can usually be made from acute urethritis cases directly, if the meatus is carefully cleansed beforehand and the cultures are made from well within the urethra. If other organisms are present, plates may be made from the same medium, and placed in the incubator in vacuum desiccators, in which the pressure is lowered 10 per cent. Good growth may be obtained on fluid mediums prepared as above except for the agar, and with or without sugar. The agar tubes should have, after hardening, a small quantity, about 0.5 c.c., of water of condensation in the lower angle of the slant. This assures the best growths.

Antiseptic Action of Local Anesthetics Against the Gonococcus. The germicidal value of certain local anesthetics in solutions of the same strength as those commonly used in clinical work was determined by E. O. Swartz.⁵ It was found that alpha-eucaine inhibits the growth of the gonococcus for the first twenty-four hours, but does not kill it. Only a few colonies survived in the 1 per cent. solution while the 0.5 per cent. solution permitted a very luxuriant growth. Beta-eucaine solutions neither killed nor inhibited growth of the gonococcus in the period of time and in the dilutions used, which were the usual concentrations of clinical work. Alypin killed the gonococcus in 5 per cent. solution but permitted a growth in the 2.5 per cent. solutions. There was no inhibitory action noted in the case of this drug. Apothesine killed the gonococcus in five minutes in strengths of 1, 1.5, and 2 per cent. or over. In 0.5 per cent. solutions, a few colonies survived. These did not appear for forty-eight hours, thus showing an inhibitory or antiseptic action even in 0.5 per cent. solutions. Benzyl alcohol invariably killed the

(5) Jour. Urology, August, 1920.

gonococcus in five minutes in strengths of 3 and 2 per cent. In one experiment, a few colonies survived immersion in 1.5 per cent. solution for five minutes. The antiseptic action of benzyl alcohol together with its lack of toxicity suggested its use as a gonococcocide in acute gonorrhea. Work along this line is being carried on at present and will be reported later.

The Action of Sodium Oleate on the Gonococcus. The bacteriolytic power of soap has been extensively investigated as the result of the demonstration that soaps are largely responsible for the bacteriolytic properties of inflammatory exudates. Its powerful effect on pneumococci led D. M. Davis and E. O. Swartz⁶ to the assumption that similar results might be observed with the gonococcus, an organism having certain characteristics in common with Fraenkel's coccus. It was found that sodium oleate is much more effective in increasing the germicidal power for the gonococcus of certain drugs than of others. With phenol and the tricrosols the increase is slight; with potassium mercuric iodide; mercurochrome-235 and mercurochrome-230, somewhat greater; with the silver compounds, chlorazene, mercurochrome-220, mercurochrome-226, and C-244 it is of a still higher order. Sodium oleate solutions can be borne in the urethra without symptoms of irritation up to a strength of 1 per cent. These experiments suggest the use of a mixture of sodium oleate and boric acid as an adjuvant to other drugs in the treatment and prophylaxis of gonorrhea. In the case of irrigations, the soap would assist the cleansing action, in addition to its germicidal or opsonic value. In prophylaxis the action of soap should be taken advantage of within the urethra as well as externally, where its value has long been taught.

Precipitin Reactions in the Diagnosis of Gonococcus Infections. A precipitin reaction in the diagnosis of gonococcus infection which is remarkable for its simplicity and which gave excellent results in a large series of cases is described by Robinson and Meader.⁷ The precipitinogen was produced by autolysis of the

(6) Jour. Urology, October, 1920.

(7) Ibid., December, 1920.

gonococcus in 0.85 per cent. of sodium chloride solution. For diagnostic purposes, this autolysate was obtained by moistening a sterile cotton swab in the suspected material and incubating in 2 c.c. of physiologic salt solution for six hours. The swab is then removed and the infusion is centrifuged until a perfectly clear supernatant liquid is obtained. Occasionally it is found that a specimen especially of vaginal origin remained opalescent in spite of continued centrifugation.

The procedure in brief is as follows: for each specimen to be examined 0.25 c.c. of diluted clear serum from two immune and one normal rabbit are placed in serologic test tubes. The clear extract of the specimen to be tested is layered over the serum in the same amount. The tubes are incubated for one hour at 37° C. and are allowed to cool before readings are made. Most of the results reported were obtained by the use of serum from rabbits injected with two strains. Two immune sera are used in the test in order to duplicate the results while the serum from a normal animal prevents reading any non-specific precipitation. In the case of some sera there appeared to be a false reaction when sterile salt solution was layered over the serum. This difficulty was overcome by diluting the serum with salt solution and centrifuging until it was perfectly clear. This diluted serum was used in both the test and the control tubes in place of the undiluted serum. The dilution used in making the tests is one to two.

Vas Puncture in Acute Gonorrhea. The treatment of acute gonorrhea by vas puncture is urged by Belfield⁸ because in the majority of cases the disease becomes urethrovessiculitis within the first month.

Medication of the acutely infected vesicles and ampullae by way of the vasa with 5 per cent. collargol solution eliminates the infection from these otherwise inaccessible cavities. For this purpose vas puncture is preferable to the original operation, vasotomy.

The prompt arrest of the vesicular infection in the acute stage averts chronic vesiculitis with its manifold evils, eliminates epididymitis, and converts the hither-

(8) Jour. Amer. Med. Ass'n., Jan. 17, 1920.

to refractory urethrovessiculitis into a urethritis only, with which we are well equipped to cope.

Before injecting the vesicle by way of the vas, the physician should master the technique either on the cadaver or through clinical observation.

Intravenous Injections of Sulfarsenol. Last year Lévy-Bing suggested the use of sulfarsenol intravenously in chronic prostatitis. This year Asch⁹ gives the result of five years' experience with the use of the sulfarsenol given intravenously. He says that the intravenous injections of this drug have a remarkable influence on the serious cases of parenchymatous prostatitis due to the gonococcus. There follows in the stools a very rapid diminution in the size of the prostate and a very rapid disappearance of the gonococci in the prostatic secretion, even in the most chronic cases.

Arsphenamine in Acute Salpingitis. Having previously observed and reported the beneficial results from arsphenamine in acute and chronic prostatitis, Lévy-Bing and Duroux¹ have made use of arsphenamine in cases of acute salpingitis of gonococcus origin. No attempt is made to explain the *modus operandi* of the medication in acute salpingitis. The authors content themselves with citing the value of this method of treatment and suggest that others make use of it.

Gelargin in Gonorrhea. The results of the use of gelargin in gonorrhea both as a prophylactic and as an abortive treatment is given by Engleson.² Gelargin is a combination of gelactose and silver, and has a silver content of approximately 10 per cent. The action of the drug on the urethral mucosa is somewhat less irritating than that of albargin or protargol. In the abortive treatment of gonorrhea, using a 1.5 per cent. solution, Engleson found it effective in 76 per cent. of fifty-one cases. In a series of ninety-two cases, used as a prophylactic in the same percentage strength he found it effective in 100 per cent. of the cases.

Towel for Urologic Work. A need for improvement in the technique of draping the penis for urologic work

(9) *Ann. des mal. vén.*, February, 1920.

(1) *Ibid.*, September, 1920.

(2) *Dermat. Zeitschr.*, March, 1920.

has long been felt. The towel employed after the penis has been cleansed is usually one with a hole in the center. Often the hole is either too small, leading to construction of the penis, or too large, resulting in the carrying of

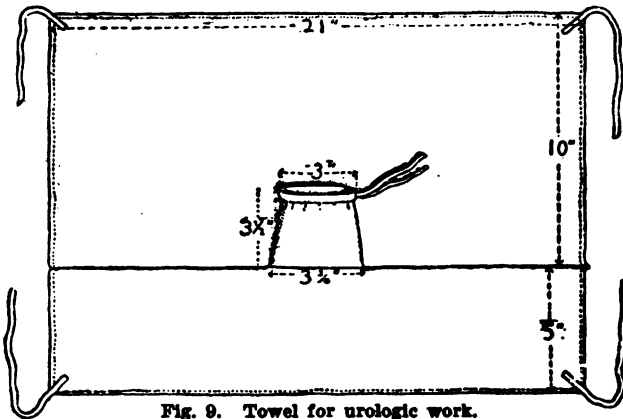


Fig. 9. Towel for urologic work.

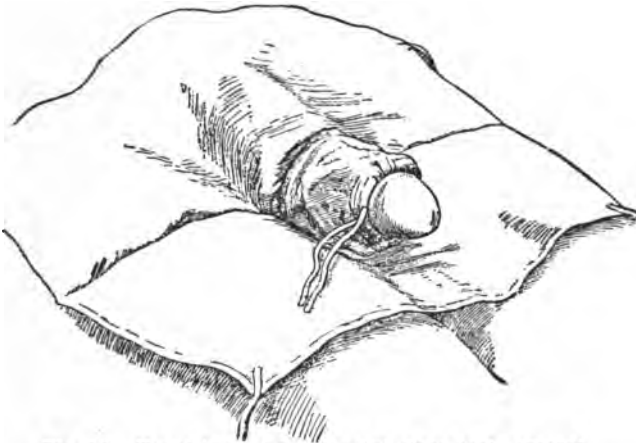


Fig. 10. Towel in use; nothing but glans penis exposed.

pubic hairs into the operative field. The use of several towels round the base of the penis is just as unsatisfactory.

A towel (Fig. 9) for urologic work is so designed by

Levy³ that it has a hole, to the edges of which is attached a conical pocket with a draw string at the apex. The measurements of the towel, as found convenient at the Hebrew Hospital, are given in the illustration. It is easily made by sewing together two corresponding pieces of material, and then making a band for the drawstring.

The penis is cleansed, and a sterile towel then placed over it. The first three fingers of one hand are introduced into the pocket; the glans penis is grasped and brought out. The drawstring is then tightened behind the glans in the coronary sulcus (Fig. 10). By this method nothing but the glans penis is exposed. The strings at the corners of the towel may be tied on either side beneath the thighs.

The towel has been employed successfully for circumcisions and for plastic work on the penis, as well as for instrumentation.

CHANCROIDS AND OTHER ULCERATIONS.

Chancroidal Infections in the District of Paris. A study by J. E. Moore⁴ of 693 venereal ulcers in the American Expeditionary Forces' clinic shows that there had been an original diagnosis of chancroid in 379 and of primary syphilis in 314 of the cases. The history of incubation, the clinical appearance of the sore and the presence of the organism of Ducrey are no more than suggestive in excluding primary syphilis. All venereal ulcers should be repeatedly examined for at least three consecutive days by dark field illumination, and local application of antiseptics or the cautery should never be practiced until these examinations have been made. All patients with chancroid should be followed by frequently repeated Wassermann reactions for at least three months. Of 135 cases so followed, a positive Wassermann developed in nineteen cases, or 14.8 per cent. Moore is of the opinion that the use of calomel ointment affords little, if any, protection against chancroidal infection. He was able to prove this by inoculating

(3) Jour. Amer. Med. Ass'n., Nov. 13, 1920.

(4) Jour. Urology, April, 1920.

patients with the bacillus of Ducrey. Three inoculations in each one of five cases were made. One inoculation was used as a control, the other was repeatedly rubbed with calomel ointment, whereas the third was treated with tincture of green soap and water. The control and the inoculation treated with calomel ointment were invariably positive, whereas the one treated with tincture of green soap and water was uniformly negative. Further evidence of the lack of protection afforded by calomel ointment is shown by the circumstances attending the exposure to the same woman of seven men belonging to one organization. On their return to camp, all took prophylaxis at intervals from the exposure of three-quarters to three hours. On the fifth day thereafter, all developed penile sores, which were typically chancroid, and which in six cases were later complicated by suppurating bubo. In reviewing the method of prophylaxis prevailing at the camp, the only discoverable fault was that no soap and water had been employed. This led to inquiry as regards the incidence of chancroid following prophylaxis as compared with venereal disease in general. It was found that in 1681 cases of venereal disease (including gonorrhea, chancroid, and syphilis), it was claimed that prophylaxis had been taken in only 720 instances, or 41.7 per cent., whereas when the inquiry was limited to the chancroid alone, 58.5 per cent. claimed to have had prophylactic treatment. Investigation of individual cases frequently showed that the feature omitted from the treatment had been the preliminary use of soap and water.

[The work of Reasoner in which was demonstrated the spirochetocidal activity of tincture of green soap, together with the evidence herewith presented concerning the bactericidal activity of the same agent against the bacillus of Ducrey leads one to the conclusion that plenty of soap and water are probably much more efficient prophylactics than calomel ointment for both the chancre and the chancroid. Moreover the bacteriolytic action of sodium oleate on the gonococcus has been demonstrated by Davis and Swartz (p. 112 this volume). Perhaps the most efficient prophylactic for all three diseases may yet prove to be soap and water.—M.]

A Cultural Method for the Diagnosis of Chancroid.

The difficulties of demonstrating the Ducrey bacillus are well known; therefore, any method which facilitates the demonstration of this organism is to be welcomed. A cultural method for the diagnosis of chancroid is described by Teague and Deibert.⁵ The method they made use of is as follows: 1 c.c. of rabbit's blood is placed in a small test tube and then either heated to 55° C. for five minutes or for thirty minutes. The authors believe that it is advisable to use one tube of each. The pus is then transferred to the tube of clotted rabbit's blood by means of a piece of stiff iron sterilized wire and is quickly distributed in the serum by passing the wire several times around the clot. The second tube is inoculated in the same way with a fresh wire. After incubation at 37° C. for from twenty to twenty-four hours, the serum around the clot is thoroughly stirred with a platinum loop and then a smear is made and stained by Gram's method. Examination of the stained smear shows characteristic chains of small Gram-negative bacilli, sometimes apparently in pure culture, sometimes together with Gram-positive cocci or bacilli. If these characteristic chains are present, it is stated that the culture is positive for Ducrey bacilli.

The authors have made cultures in the manner described in 274 penile ulcers. At most of the clinics it was requested that cultures be made of all sores regardless of whether they were clinically chancroid or not. Inasmuch as more than 50 per cent. of the sores cultured were positive for the Ducrey bacillus and inasmuch as most of the negative cases showed no clinical evidence of chancroid, it follows that a diagnosis of chancroid could be made by means of this method in a very large percentage of the cases, probably above ninety per cent. This result can be obtained without applying any special dressing the day before culturing and in most cases without interrupting the usual routine treatment at the clinic.

Chancroid of the Nares. Localization of the chancroids in the nares is an unusual observation but when one considers the opportunities of carrying contagion

(5) Jour. Urology, December, 1920.

from the penis to the nose in the process of picking the nose, it is rather surprising that we do not see the localization in the nose more frequently.

The patient reported by Milian⁶ presented a number of lesions on the penis. At the same time he presented a lesion in the nares on the left side. Microscopic examination was made to determine the nature of the penile ulcerations and it was found by auto-inoculation that the Ducrey bacillus was present in great numbers. Eventually the organism from the nasal lesion was inoculated likewise in the arm of the patient and the typical chancroid developed. The striking feature of the case was the marked discomfort occasioned by the nasal lesion which was much greater than that occasioned by the penile lesion.

Pseudo-Chancres of the Lips. During the war lesions due to the fusiform spirillum of Vincent were observed in great numbers in various parts of the buccal mucous membrane. Two lesions on the lips of a native were observed by Jamin⁷ of Tunis. Before coming under the observation of the author the lesions had been examined by several men and a diagnosis of primary syphilis had been made. Each of the ulcerations was markedly irregular and beneath the crusts which covered the lesions the ulcerative process was exactly the same. This consisted of a true ulceration with very irregular borders and a yellowish color which strongly suggested the soft chancre. The floor of the ulcer was dark red, secreting an abundant thick pus which dried in heavy crusts and bled rather freely. On the mucous membrane which came in contact with the saliva the lesion was less vegetative, did not bleed, nor was there a pseudo-membrane. Both ulcers were on a markedly indurated base which was very tender. In fact both lips were swollen and sensitive to the touch. The buccal mucous membrane was apparently normal in appearance, as were also the teeth. There was submaxillary adenopathy, which was painful and tender. There was no history of syphilis and the Wassermann reaction was negative. Dark field

(6) Bull. soc. franc. de dermat. et de syph., 1920, No. 7.

(7) Ann. de dermat. et de syph., June, 1920.

examination was negative for *Spirochæta pallida*, but the large, thick *Spirillum* was present in great numbers.

The treatment consisted of one intravenous injection of arsphenamine. Locally there was application of methylene blue. Cicatrization took place very rapidly and within a week the patient was practically well.

Treatment of Chancroid. The results of the use of a method first suggested by Jersild of Copenhagen and later used by Robbins and Seabury is described by Jacob,⁸ who treated fifty-two cases by this method and is convinced that the results are unusually good.

A 25 per cent. solution of copper sulphate in distilled water is applied to the sore and then the short high-frequency spark from a rather fine-pointed vacuum electrode is applied directly to the lesion for from one to three minutes, depending on the extent of the ulceration. Especial care is exercised in carrying the point of the electrode well down into any fissure or undermined edge, and the area of application should extend over the edge of the sore about one-sixteenth of an inch into the doubtfully healthy area. The lesion is then dusted over with powder and the patient is instructed to return in two days. If the ulcer is not granulating properly, the treatment is repeated. Later, to promote healing, silver nitrate, in spirit of nitrous ether and distilled water is applied from time to time.

Ulcerating Granuloma of the Pudenda. A review of the literature with a bibliography and some observations on the disease as seen in Porto Rico is made by Herman Goodman.⁹

A personal survey of over 12,000 men and 900 women disclosed only four cases of ulcerating granuloma. No case was seen among the soldiers at Camp Las Casas. Two of the cases were studied histologically and the findings were the same as those transcribed from the histologic studies of Galloway. In three of the cases *Calimotobacterium granulomatis* has been demonstrated for the first time in the United States or its dependencies. In one case the spirochetal organisms described by Wise were found. Goodman believes that there are two dis-

(8) Archiv. Dermat. and Syph., April, 1920.

(9) Ibid., February, 1920.

eases bearing the same name, clinically so similar as to defy differentiation. The disease is not syphilis, although it may be associated with syphilitic lesions or be present in a Wassermann-positive syphilitic free of syphilitic manifestations. Arsphenamine and mercury are ineffective in its treatment. Antimony and potassium tartrate (tartar emetic) was not given a sufficiently thorough trial to warrant any positive expression of its efficacy. The finding of only two cases among 900 prostitutes proves that the danger of infection at the present time in Porto Rico is slight, but should not be entirely disregarded. Quarantine measures should certainly be introduced to prevent the transfer of the infection, especially to our southern ports, either from Porto Rico or from South American countries.

Erosive Vulvitis. The disease of men known as erosive and gangrenous balanitis has been recognized for a number of years. The same disease occurring in women as erosive and gangrenous vulvitis is not generally recognized. Three such cases have come under the observation of T. L. Driscoll,¹ of the United States Public Health Service.

The predisposing causes seem especially to be filth and prostitution, with attending frequent copulation and exposure, and unnatural sexual relations. All three women were inmates of the jail in Richmond, Virginia, and all had been convicted of prostitution. The diseased genitals were extremely dirty, with a large amount of discharge from the focus as well as from the vagina, and presented ideal conditions for the growth of the specific organism. In each instance there was extensive ulceration of the part with a slight amount of local edema. Two of the cases presented an inflammatory involvement of Bartholin's gland, whereas the third gave a history of such an involvement two years before (Plate XIV).

The organisms isolated in each instance were the typical spirochete and vibrio growing in symbiosis as described by Tunncliffe. The spirochete averaged from 5 to 30 microns in length, had very rapid motion, was Gram-negative and took ordinary dyes well. It had an

(1) Archiv. Dermat. and Syph., February, 1920.

especial tendency to grow in the more superficial of the diseased parts.

In all three cases the inguinal lymphatic glands were involved. On palpation they were hard, nodular and moderately enlarged, but there was no suppuration. No systemic changes of pathologic significance could be noted. The duration of the ulceration ranged from eight months to three years. Local pain and discomfort with violent itching seemed to be constant factors. Dysuria was more or less marked. All the patients had a foul smelling leukorrhea since the date of onset, and the discharge preceded the vulvar condition in at least one instance. Generally there appeared to be a slight degree of toxemia, and the patients showed some degree of melancholia. In each of the three cases the Wassermann reaction was negative. There was no response to antisypilitic treatment, including arsphenamine. In each case the characteristic spirochete and fusiform bacilli were isolated from the serum of the ulcers.

Modification of the Fontan Method for Treating Bubo. In 1918 the results of the work of Dubreuilh and Mallein² were noted with a modification of the Fontano method which consists in an evacuation of the bubo and replacing the pus evacuated with vaseline containing 10 per cent. of iodoform. In 121 cases there were 106 complete successes and fifteen cases which were only partially successful.

Bodin³ presents the results of his work with thirty-five cases of bubo, using the method as described by Dubreuilh and Mallein. Of the thirty-five patients treated, he succeeded in curing twenty-four or 68 per cent. in six days. He advises beginning the treatment just as soon as fluctuation is felt. In some cases the failure of the incision to close is manifested. In such cases he advises a rather radical incision and then treatment of the abscess which results. Bodin states that this method of treatment is the most satisfactory which he has yet used.

Chronic Balanitis Simulating Epithelioma. Well defined areas of chronic dermatitis are frequently en-

(2) Practical Medicine Series, 1918, Vol. VII, p. 170.

(3) Ann. de dermat. et de syph., March, 1920.

countered in men past middle age. Thibierge⁴ reports the case of a man 51 years old who had on the upper part of the glans penis a number of small, well-defined plaques of a smooth, uniform surface and a brilliant deep red. The lesions were perfectly dry and appeared to Thibierge to resemble the cases recorded by Queyrat under the name of *erythroplasie*, and by Darier under the name of "flat epithelioma of the glans." However, infiltration was noticeably absent and the patient affirmed that some of the lesions had cleared. Under simple application the lesions had improved considerably in appearance. The patient was apparently free from syphilis and no sugar had been found in the urine. In the opinion of the author, this case presented a chronic balanitis independent of diabetes and syphilis which could be attributed to seborrhea. There were also lesions present on the face of the patient. In the opinion of Darier, this ought to be termed a pre-epitheliomatous dermatitis. He believes that in such cases early operation should be resorted to.

Preputial Gangrene. Since the work of Fournier it is well known that gangrene of the prepuce may occur without any pre-existing pathologic process. As a rule, however, the gangrene is preceded by chancreiform lesions or a chancre. Four cases of lesions of this type are reported by Block and Schulmann.⁵

The cases may be divided into four types according to the course they take.

First, the plaque of gangrene is simple and yields to treatment with *restitutio ad integrum*.

Second, perforation of the prepuce with penetration.

Third, spontaneous but incomplete circumcision.

Fourth, spontaneous and complete circumcision.

The cases were all studied bacteriologically. Numerous organisms were found but only two occurred constantly in all the cases. One of these was *perfringens*; the other was *hystoliticus*.

Various reasons are given as contributing factors in the development of gangrene of the prepuce. Among these may be mentioned alcohol and lowered nutrition.

(4) Bull. soc. franc. de dermat. et de syph., 1920, p. 157.

(5) Ibid., 1920, p. 62.

In the four cases cited these factors did not enter. In the opinion of the authors, the elasticity of the tissue of the prepuce is probably the most important factor in the development of gangrene.

The treatment consisted of neo-arsphenamine both locally and intravenously and applications of hydrogen peroxide freely. All the patients made uneventful recoveries.

Veneroid Ulcer. Welander in 1903 reported, as a definite clinical entity, a disease occurring in the form of ulcers about the vulva and genital region in girls and women who had not been exposed to venereal disease. Over half of his twenty cases occurred in young girls or young women with intact hymen.

Olson⁶ has had the opportunity of studying a case of veneroid ulcer and reports in detail his observation.

The patient, who was a woman, 21 years old, noticed a small sore or ulcer on the inner surface of the right labium minus, Oct. 1, 1919, which caused some pain on walking. The sore or ulcer secreted a gray, rather sticky discharge. In a few days two more ulcers appeared on the labia majora. Constitutional symptoms, such as fever, and malaise, were absent. The ulcers were superficial, sharply circumscribed, depressed in the center and covered with a sticky gray discharge. There was no areola and no surrounding inflammatory reaction. The ulcers were about the size of a dime, those on the labia majora being almost perfectly round, while that on the inner labium near the hymen was somewhat oval. There was no induration and the inguinal glands were not enlarged.

The patient denied exposure to venereal disease, and the hymen was apparently intact. Repeated examinations for *Spirochaeta pallida* by dark field and staining methods gave negative results. Ducrey's bacillus was not found, although a number of slides were made at intervals of a few days. The spirochete or spirillum and fusiform bacillus of erosive vulvitis were absent. Examination for the diphtheria bacillus likewise proved negative.

The technique in scraping the ulcers and applying

(6) Archiv. Dermat. and Syph., March, 1920.

alcohol in order to obtain serum for the examination for *Spirochaeta pallida* proved markedly beneficial, and the ulcers healed under indifferent treatment in about a month, leaving round, slightly depressed scars with raised edges.

The ulcer is round or oval and is usually about the size of a dime. It is rather superficial and covered with a grayish or slightly yellowish mucopurulent discharge. The edges are raised, sharply defined and are not undermined. There is no areola and there are no signs of inflammation in the adjacent tissues. On palpation there is no sign of induration. The lesions are rather painful when touched or scraped with a dull instrument and bleed readily. There is no outpouring of serum as in the primary lesion of syphilis. In a general way the ulcers resemble chancroid, chancres and moist papules of syphilis. The ulcers are acute in character, come on suddenly, and heal under indifferent treatment in about a month. The inguinal glands, although as a rule not enlarged, are occasionally slightly enlarged. The scars, which soon after healing are quite characteristic, are superficial, round or oval with raised edges. In time, undoubtedly, these scars become almost, if not entirely, unnoticeable.

Microscopic examination is of great importance, as it is necessary to exclude, by repeated examinations, *Spirochaeta pallida*, the bacillus of Ducrey, Vincent's spirochete and fusiform bacillus, and the diphtheria bacillus.

In contradistinction to the findings in chancroid, Welanders in many experiments obtained negative results when the pus from these ulcers was inoculated on the arm of the patients. In other words, the disease is not auto-inoculable. No cases have been reported in which the husband has become infected. The infectivity of the disease, therefore, appears to be slight.

While there are a number of distinct dissimilarities, the general appearance of veneroid ulcer is strikingly similar to that of chancroid and the chancre. In the diagnosis of veneroid ulcer, the history of non-exposure to venereal disease is of great importance. This history is often corroborated by such evidence as the age of the girl and her general appearance. Proof of non-expo-

sure is not infrequently found in the presence of an intact hymen. With a history of non-exposure to venereal disease, an acute onset, absence of constitutional symptoms, and the characteristic depressed, superficial, round or oval ulcer with no induration, a probable clinical diagnosis of venereum ulcer can be made. The probable or tentative diagnosis is made certain by the exclusion, on repeated examination, of *Spirochaeta pallida*, the chancreoid bacillus, the diphtheria bacillus and the spirochete and fusiform bacillus of erosive vulvitis.

SYPHILIS.

THE CHANCER.

Bacteriologic Examination of Chancres. The fact that a clinical differentiation can not be made between chancreoids and chancre is well shown by the work of Belgodère.⁷ The report represents the work done in a military hospital in which there were observed 1652 cases of contamination but owing to the retention of the records by the military authorities, records of only 267 cases of chancre are available for the report.

All of the cases observed were examined for the bacillus of Ducrey and *Spirochaeta pallida*. For the one the phenolthionine and for the other the silver nitrate impregnation method of Fontana-Tribondeau were used.

The 267 cases of chancre were as follows: the chancreoid, 125; chancres, 73; mixed chancres, 17; and 52 cases in which the microscopic examinations for both were negative.

In the syphilitic lesions, *Spirochaeta pallida* was found in seventy-three cases. There were seventeen cases in which both of the organisms were found, and seventeen cases in which the results of both were negative; therefore, in about 85 per cent. of the cases, *Spirochaeta pallida* were demonstrated in a known chancre.

A bacteriologic examination of the soft chancre resulted in 81 per cent. positive finding. This proportion can be brought up to 100 per cent. if the examination

(7) Ann. des mal. vén., October, 1920.

be made in the first two days and if no treatment has been instituted. The bacillus of Ducrey is usually seen in the form of "chainettes" and this is the most common form in all the periods, particularly when the chancroid is in full evolution, which is between the tenth and twentieth days.

Intracervical Chancre. If one has the patience to wade through the article by Belgodère⁸ he will read concerning the *respectability* (which he italicizes all through the article) of a certain demobilized American who developed a penile chancre and because of this exaggerated sense of *respectability* sought the advice of a druggist who treated him for some time. The foregoing has nothing in particular to do with the case except that the woman with whom the patient cohabited developed an intracervical chancre.

[The author seems to imply that the *respectability* of the American was to blame for the intracervical chancre of the *montmartroise*. No mention is made of the respectability of the woman who cohabited with the excessively respectable American. Perhaps her *respectability* was not worthy of comment.—M.]

Chancre of the Gum in a Man Without Teeth. A chancre of the arch of the palate and of the gum was observed in a man of 45 by Gastineland Legrain.⁹ The patient was a shoemaker working in a rather large shop where the practice was to hold the tacks in the mouth. After having the tacks in the mouth for a time it not infrequently happened that the tacks were replaced in the boxes. The workmen were of the itinerant class, and it is probable that some one with mucous patches had had tacks in his mouth, and these same tacks were later taken up by the patient.

Chancre of the Little Finger. Chancre of the little finger is one of the rarest of the extragenital lesions. Queyrat¹⁰ had occasion to treat a young woman who developed a lesion at the junction between the distal and second phalanges and palmar surface of the little finger of the right hand. The lesion was typical in appearance and the usual epitrochlear and maxillary glands on that

(8) Ann. des mal. vén., December, 1920.

(9) Bull. soc. franc. de dermat. et de syph., 1919, p. 311.

(10) Ibid., 1920, p. 55.

side were present. The patient was 18 years old and gave a history of having cut her finger on a mandolin string. It became slightly secondarily infected and remained open for some little time. She admitted that during this period of infection she had allowed her hand to stray over the genitalia of a young man who was courting her. One month later the lesion, which had in the meantime healed, recurred and rapidly developed into a typical chancre.

Statistical Study of Extragenital Chancres. A statistical study of the cases of extragenital chancres seen during a period of fourteen years at Barnard Free Skin and Cancer Hospital in St. Louis is made by Porter.¹ During this period 225 individuals having chancres were examined; among these were fifty-five extragenital lesions giving a much higher percentage (24.5 per cent.) than that of any other observer. The location of the lesions were as follows:

Lip: upper	9
lower	22
	—
Tongue	31
Eyelid	6
Cheek	2
Angle of mouth.....	1
Nose	1
Temple	1
Forehead	1
Tonsil	1
Thumb	2
Breast	2
Abdomen	2
Anus	2
	—
Total	54

Only nine patients were able to state the source definitely. Four of the lip chancre patients gave a definite history of having kissed an infected person, and one gave a history of having received a bruised lip in a fist fight with a syphilitic. Both breast cases traced their infection to having nursed babies whom they later found to have hereditary syphilis. The other two were thumb

(1) Archiv. Dermat. and Syph., January, 1920.

PLATE XIV.



Erosive vulvitis.—Driscoll, page 121.



cases. One patient was a midwife, who, while acting in her official capacity, sustained a cut thumb and immediately afterward the umbilical cord was broken, and her hand was covered with the blood. The other, with three chancres on the right thumb, appeared with teeth marks showing at the borders of each of the three lesions, the proof of having been bitten by a man, who, he said, bit him purposely to infect him.

As has been the rule elsewhere, the number of lip chancres predominates. Montgomery gives his maximum percentage, including four at the angle of the mouth, as "over 49 per cent.," while the author's figures show 56.3 per cent. of the total extragenital lesions. Sex did not seem to play such a large part in the cases as it did in other instances where the male, by reason of his greater "social freedom," had the higher percentage. In accordance with other writers, married women lead the percentage in lip chancres with the single male a close second, but of the total thirty-one lip lesions, sixteen males and fifteen females were afflicted.

These figures also lead Montgomery's in the frequency of the lower lip lesion; 70.9 per cent. are found here as against his 56.4 per cent. of total lip primaries. In outline, the division is as follows:

Chancre of the Lip.

	Male	Female
Lower lip	10	12
Upper lip	6	3
Married	4	8
Single	7	2
Status unknown	5	5

Next to the lip, the tongue shows the greater number of lesions. This can be explained in the same manner as the high percentage of extragenital lesions—*i. e.*, the cases were sent here for a final diagnosis with the provisional diagnosis of cancer of the tongue or else were selected cases for demonstration purposes.

Chancres not located on the head are equally divided, and do not furnish much of interest outside of the locations of two, both in the perineum. One was in a colored girl, single, aged 20, who had a hard chancre superimposed on a hemorrhoid. The other, a white boy, aged

9, was sent there by the school authorities with a letter of introduction which asked for a definite report, as they "wanted to punish the guilty parties." The boy entered the hospital with gonorrhea and a hard chancre which was located in the anus and extended up into the rectum. His father, an ignorant Italian, removed him from the hospital three hours later, and the patient has not been seen since.

The principal points as regards the sex of these patients have already been enumerated under the discussion of the lip chancres. The total figures on this subject give thirty-one males and twenty-four females, the percentage being 54.5 and 45.5, respectively. These percentages agree very closely with those of Montgomery who, in computing percentages of 410 cases, finds 56.5 and 43.5 in the two sexes.

The social status of but forty of the patients is available from the records, and of these 60 per cent. were married and 40 per cent. single. Here again, as in the lip chancre figures, the single male and the married female are in the lead, with twelve single males and ten married males, to four single females and fourteen married females.

There was a high percentage, as before, in the high rate of infection of the colored race, namely 18.1 per cent. of the total extragenital lesions. In spite of the fact that the negro is not supposed to be addicted to kissing in his amours, the cases were nearly all lip chancres.

It is interesting to note that the majority of infections occurred during the third decade. There were three each before the age of 10 and after the age of 50. From 10 to 20 there were nine; from 20 to 30, twenty-two; from 30 to 40, ten; and from 40 to 50, five. This gives 73 per cent. occurring between the ages of 16 and 35.

Syphilis and the Mosquito. The fact that yellow fever and malaria are transmitted solely by mosquitoes has led Belgodère,² as the result of a case observed and studied by him, to believe that in some cases syphilis may likewise be transmitted by the mosquito.

The patient was a young artilleryman whose veracity,

(2) *Ann. des mal vén.*, June, 1920.

according to the author, was not to be doubted. The patient denied all exposure and stated that on one occasion while serving his gun he was bitten on the back of the hand by a mosquito. The resulting excoriations following constant scratching did not heal and continued to give him trouble for some time. Eventually typical secondary eruption of syphilis appeared and was observed by the author.

[The mosquito probably will never play a very important rôle in the transmission of syphilis. There are too many other and more efficient means of contamination.—M.]

REINFECTION.

Syphilitic Recurrences and Reinfection. Reinfections and recurrences in syphilis are constantly occupying the attention of syphilographers now that we have such efficient therapy in our hands, namely, the intravenous injections or arsphenamine. Two cases which are of interest are reported by Saraphi.³

The first case occurred in a man of 25, who had a typical group of chancres on the penis and a secondary eruption and who was given two intravenous injections of arsphenamine followed by thirty mercurial injections. He left the hospital and five months later returned with two lesions in the site of the former chancre and a roseola. There had been no other treatment. The author is unable to state that this is a reinfection, but the evidence supports that view.

The second patient was a man 22 years old who received very intensive mercurial and arsphenamine injections consisting of a series of nine injections constituting 11 grams of arsphenamine in all. The Bordet-Wassermann reaction became completely negative. One month after his last mercurial injection he developed a typical chancre on the penis. Microscopical examination showed *Spirochaeta pallida* in great numbers. The chancre developed twenty-seven days after the last exposure and promptly yielded to two injections of arsphenamine. The author is convinced that the intensive

(3) Ann. des mal. vén., July, 1920.

treatment together with the negative Wassermann make it impossible to look upon this case as a recurrence and that it is a definite case of reinfection.

SPIROCHAETA PALLIDA.

Improvised Dark Field Apparatus. According to Coffin,⁴ a piece of passe-partout or black paper, the size of a quarter, pasted on the bottom of the Abbe condenser of the ordinary microscope will make a dark-field ap-



Fig. 11. Method for demonstrating *Spirochaeta pallida*: A, side view of Abbe condenser; arrow points to black paper; B, bottom view.

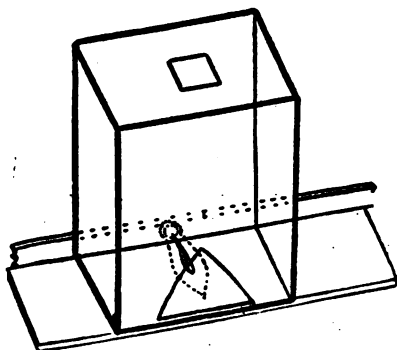


Fig. 12. Hood for light.

paratus for examinations for *Spirochaeta pallida*. The author has employed this method for six months, and has found it even better than the regular "dark field" attachment sold for the purpose.

A hooded light of 100 watts, about 8 cm. above the work bench, is employed. A piece of black passe-partout binding, the size and shape of a quarter, is pasted on the center of the lower (convex) surface of the Abbe condenser, the top of which should be level with the top of the stage of the microscope. The high (4 mm.) objective in used (Figs. 11 and 12).

(4) Jour. Amer. Med. Ass'n., May 22, 1920.

The light is regulated with the lower shutter of the condenser till the field looks like the clear sky on a moonless night. Two fields will be found; one should rack slowly through the first field to the second, where *Spirochaeta pallida* will be beautifully demonstrated.

Toning and Fixing Silver-Stained Spirochetes. Silver-stained spirillar organisms rapidly deteriorate and in order to obviate this Perrin⁵ has made use of the well-known photographic process of toning the stained preparation with gold and sodium chloride and fixing with sodium hyposulphite. The formula used to stabilize the preparation is as follows:

	Gm.
Sulphocyanide of ammonium.....	6.25
Tartaric acid (or citric acid).....	0.50
Sodium chloride	1.25
Water	250.00
Solution of gold chloride 1:100.....	6.25

By this method the silver-stained organisms are permanently fixed and can be used indefinitely for teaching and other purposes.

Unity of Syphilitic Virus. The question of unity or the duality of syphilitic virus is again opened by the recent work of Marie and Levaditi. These men are strong partisans of the duality theory. Sicard⁶ is unable to accept the duality of the syphilitic virus and states his objections *in extenso*. He admits that there are analogies with various organisms, particularly with the bacillus of tuberculosis and the bacillus of leprosy, but he is convinced that these differences in the bacilli are due merely to temporary changes due to their proliferation in different kinds of tissue and that essentially the bacillus is the same, regardless of whether it has invaded the central nervous system or the skin.

If one supposes the spirochetes have an exclusive affinity for the nervous system, in other words, a neurotropic spirochete, these organisms could not be transmitted from one person to another except during the period of the chancre, inasmuch as the cutaneous and

(5) Archiv. Dermat. and Syph., September, 1920.

(6) Presse méd., 1920, p. 513.

mucous lesions are, by the very definition, the extreme exception. Such an organism, therefore, is destined to disappear, because the opportunities for contagion are rare; but as a matter of fact syphilis of the nervous system is on the increase rather than the decrease.

It has been maintained that the central nervous system infections might be somewhat modified by inoculation with the dermatropic organism. In attempting to demonstrate this, Sicard inoculated two paralytics with supposedly dermatropic strains, but in neither case was there successful inoculation.

According to the dualists many cases of central nervous system infection have resulted from a given source of contamination. The possibility of proving these clinical observations are remote and, moreover, it is impossible to determine whether the individual who is the source of the contamination has been infected originally with the neurotropic or the dermatropic strain. Moreover, the clinicians have constantly observed that patients who develop central nervous system infections have relatively fewer cutaneous lesions, and that in the tropics and subtropics syphilis usually remains essentially a cutaneous disease.

[Montpellier in the past two years has shown that infections of the central nervous system in the natives of Algiers occurs in about the same relative frequency as in Europeans.—M.]

Another point maintained by the dualists is the refractoriness of tabes and paresis to therapy on one hand and the readiness with which hemiplegia yields on the other. This is easily explained by the fact that in one case it is an infection of the deep parenchyma, whereas in the other it is a vascular lesion to which the medication has ready access.

Sicard's conclusion is that the organism is one and the same and that it is merely modified by the terrain on which it evolves.

Duality of Syphilitic Virus. The paper of Sicard is taken up in detail by Levaditi and Marie.⁷ They point out that it has been repeatedly observed experi-

(7) *Presse méd.*, September, 1920, p. 646.

mentally that strains isolated from central nervous system cases and those from cutaneous cases react differently when inoculated into the rabbit. The neurotropic strain differs from the dermatropic strain in the following ways: First, the neurotropic leads to papulo-squamous lesions instead of orchitis and an indurated chancre; second, by the marked affinity for epithelial cells; third, by the extremely long incubation period; fourth, by the slowness and spontaneous disappearance of the lesions; fifth, by its absence of virulence for man and monkey when inoculated cutaneously—the dermatropic organism, on the other hand, retains its virulence even after repeated passage through the rabbit; sixth, and finally, by the difference in its behavior in crossed immunity. The animals cured of a neurotropic infection and therefore vaccinated against this infection, are still susceptible to the dermatropic organism, and *vice versa*.

The authors admit that there is only one variety of the syphilitic organism, but that there are two strains of this organism, a fact which is entirely in keeping with analogies of other organisms. These strains differ in their biologic behavior, in their virulence and in their antigenic properties. The writers take up in detail the points made by Sicard and attempt to answer the objections made by him. They do not insist that the neurotropic organism invades only the central nervous system, and therefore there is no reason why that organism can not be constantly carried from one individual to another. They do not maintain that crossed immunity occurs in man.

In a meeting of the *Société française de dermatologie* the question was raised by Marie and Levaditi concerning the duality of syphilitic virus and led to a discussion in which a number of men took part. Leredde rejected the conception of the duality of the specific organism, whereas Queyrat was inclined to accept it. Renault⁸ having made two observations reported them briefly. One patient was an adjutant in whom there was a particularly grave cutaneous manifestation of the infection

(8) Bull. soc. franc. de dermat. et de syph., June, 1920, p. 183.

when first seen: The man was much concerned about his condition and followed the treatment carefully but, unfortunately, it was before the days of arsphenamine. At the end of the third year the first signs of tabes appeared. Another young man who was treated by Fournier himself had a virulent cutaneous infection which subsequently, in spite of intensive treatment, invaded the central nervous system.

Balzer did not deny the differences of different strains of spirochetes and was quite disposed to admit the hypothesis of Marie and Levaditi. Milian also was inclined to accept the theory of the duality of the virus. He stated his belief that it is not sufficient that a strain be neurotropic in order to produce tabes or paresis. In a tabetic one rarely finds typical gummas but leukoplakia is frequently encountered. Tabes and leukoplakia are lesions of a similar nature. In other words, they are lesions produced by a strain which is sclerotic rather than destructive, and it is this quality which creates the particularly marked resistance of the lesions to treatment. Inoculation of leukoplakia tissue into the testicle of a rabbit produces lesions analogous to those described by Levaditi with the blood of paralytics.

Co-existence of Tabes and "Quaternaires" Syphilides. An interesting case of tabes in which there occurred superficial luetic lesions is reported by Simon.⁹ The patient had had a chancre on the lip nineteen years prior to coming under observation. On the abdomen and on the arms were superficial lesions of the type described as quaternary—having some of the characteristics of the secondary lesions in respect to the superficiality and of the tertiary lesions in regard to the multiformity. The case is of interest because of the recent discussion concerning the dualism of syphilitic virus or the two strains of *Spirochaeta pallida*; namely the neurotropic and the dermatropic. In this case it is possible to conceive of a double infection of both neurotropic and dermatropic strains.

[Beeson recently demonstrated a case of tabes with a large, typical tertiary syphilide over the back before the Chicago Dermatological Society.—M.]

(9) Bull. soc. franc. de dermat. et de syph., 1920, p. 138.

EXPERIMENTAL SYPHILIS IN THE RABBIT.

Dissemination of *Spirochaeta Pallida* from the Primary Lesion. The value of excision of the chancre has long been a question for debate. It has been practiced rather extensively at some periods and in some clinics, whereas other workers have maintained that by the time the chancre is developed dissemination of the spirochetes already has been accomplished. An attempt was made by Brown and Pearce¹ of the Rockefeller Institute to obtain some data on the time of dissemination by a systematic determination of the presence of spirochetes in the inguinal lymph nodes and the circulating blood of rabbits at various intervals after scrotal or testicular inoculation. The organisms used in these experiments were old strains which have been maintained in rabbits for seven or eight years. The method used for determining the infection of the regional lymphatics was the incision of the inguinal nodes of rabbits which had been inoculated by the introduction of a small bit of infected tissue into the scrotum and the injection of an emulsion into the testicle in normal rabbits. It was found in a series of twenty-three animals that the extension of the material to the inguinal lymph nodes antedated both the appearance of the initial lesion and the occurrence of definite alterations in the nodes themselves, and that this occurred constantly within a period of less than forty-eight hours from the time of inoculation. Supplementing the observations on invasion of the lymphatics, a series of experiments was carried out to determine the time and frequency of blood-stream invasion. The mode of determining the presence of the *Spirochaeta pallida* in the blood was by bleeding from the heart, defibrinating and injecting 0.5 c.c. of blood into the testicles of normal rabbits. By this method it was found that spirochetes were constantly present in the circulating blood by the time the infection could be recognized by inoculation. In order to cut down the time as much as possible ten rabbits were inoculated in the right scrotum only, and forty-eight hours later the entire scrotum and testicle of this side were amputated under ether an-

(1) Archiv. Dermat. and Syph., October, 1920.

esthesia. In spite of the complete removal of a wide zone of tissue surrounding the area of inoculation, all of these animals developed syphilitic lesions, thus showing that true infection of parts outside of the zone of inoculation had taken place within the brief period of forty-eight hours.

Immunity Developed by the Local Reaction to Syphilitic Infection. Continuing their excellent work on experimental syphilis in the rabbit, Brown and Pearce² compared the results of unilateral with bilateral inoculation in the scrotum and in the testicle, also unilateral and bilateral castration after inoculation; and suppression of the primary reaction by the use of therapeutic agents and complete prevention of a primary reaction.

Of twenty rabbits inoculated in both testicles, fourteen were castrated and six were held in control. Generalized lesions developed in one of the six controls and in thirteen of the fourteen castrated animals within the period of observation.

Twenty-seven rabbits were inoculated in one testicle only; fourteen of these were castrated and thirteen were held as controls. In this series, generalized lesions developed in eight of the thirteen controls as contrasted with one of six animals inoculated in both testicles and again in thirteen of the fourteen castrated animals. The results of these experiments demonstrate conclusively that by inoculating one testicle instead of two, the incident of generalized lesions is markedly increased. When the reaction at the site of inoculation was further reduced by early removal of the infected organs, generalized lesions developed in almost every instance.

In a second set of experiments, the effects of suppression of the testicular lesion by the use of a therapeutic agent was also tested. Working with arsenophenyglycyl dichloro-m-aminophenol, it was demonstrated that by properly gauging the dose of this drug so as to suppress the lesion present without destroying the infecting organism, the infection could be intensified in the same way as by an excision of the primary lesion.

In another set of experiments, the reduction of the reaction at the site of inoculation was completely prevented

(2) *Archiv. Dermat. and Syph.*, December, 1920.

by excising the scrotum and testicle of the side inoculated within forty-eight hours after inoculation. By the end of the seventh week, eight of the ten rabbits which had been castrated in this way showed a marked generalized syphilis, and the other two developed generalized lesions at the end of two and a half months.

Primary Infection in the Testicle. A study by Brown and Pearce³ was made of the infections produced in rabbits inoculated in the testicles with two strains of *Spirochaeta pallida* which had been carried in rabbits for several years. Infection resulted in all instances; the incubation period varied as a rule between two and six weeks and under properly chosen conditions could be reduced to approximately three weeks or less.

The resulting infection pursued a typically cyclic or relapsing course which affected both the spirochetes and the associated lesions in the testicle. The spirochetes in the local lesions exhibited periodic changes less marked and less regular but identical in character with the changes which occur in the blood in cases of relapsing fever. The lesions in the testicle also showed periods of active development and quiescence or regression which followed closely upon the changes exhibited by the spirochetes.

The specific reaction in the testicle showed considerable variation in the speed and sharpness with which successive phenomena occurred as well as in the character and extent of the processes themselves. These reactions were of two fundamental types. In one group of animals, the reaction was characterized by an intense cycle of acute exudation and infiltration with a lesser degree of proliferation, followed by crisis and subsequent recurrence of secondary cycles of proliferative reaction of a minor degree. In the other group of animals, the reaction was more chronic in character and consisted largely of infiltration and proliferation. The progress of the reaction was more gradual, and sharp alterations in its course were absent. The infection progressed by a succession of stages with slight and irregular remissions.

In a third group of animals, the reaction was subacute, combining at the same time the processes of exudation,

(3) Jour. Exper. Med., April, 1920.

infiltration, and proliferation. The first cycle of reaction was fairly acute and terminated in a definite crisis with moderate regression which in turn was followed by recurrence and more or less pronounced secondary cycles of proliferation.

In all cases of outspoken infection, there was diffuse involvement of testicle, tunic, epididymis, and cord, but as the infection progressed, the lesions underwent many transformations, so that a variety of lesions was formed from processes which in the beginning were of a common type. Eventually, the reaction became more irregular and the infection became centered in one or more foci which were commonly situated in the epididymis, tunics, scrotum, or mediastinum testis. These centers served as residual foci of infection.

The duration of the testicular process was found to be very variable. In some animals, the entire reaction consisted of but a single sharp cycle, and the local infection was terminated by crisis within four to six weeks after inoculation. As a rule, the period of active infection was from two to four months, and quiescent or inactive lesions not infrequently lasted for from four to six months. In exceptional instances, local infection persisted for more than a year.

Scrotal Lesions and the Character of the Scrotal Infection. From a study by Brown and Pearce⁴ of the reaction to scrotal inoculation with *Spirochaeta pallida* in a large series of rabbits, it was found that the specific reaction presented the following characteristics.

In general, the reaction in the scrotum became apparent within from seven to fourteen days after inoculation but was subject to considerable variation. The early reaction took the form of an edematous swelling and congestion associated with a new growth of vessels or of an infiltration with more or less proliferation of fixed tissue cells. These reactions were either confined to a small circumscribed area of the scrotum or were of a diffusely spreading character, and as the infection advanced, the infiltration and proliferation together with such secondary changes as exfoliation, necrosis, and ul-

(4) Jour. Exper. Med., June, 1920.

cerations became the most conspicuous features of the reaction.

The course of the reaction in the scrotum was essentially the same as that in the testicle; that is, it was periodic in character and was marked by a phase of active progression followed by quiescence or regression and renewed activity.

The scrotal reaction resembled that in the testicle also in the varying character of the reaction, appearing at times as a circumscribed focus of reaction and later becoming diffuse, or first as a diffuse reaction which subsequently became more localized.

The lesions produced in consequence of this reaction were of two general types—one a circumscribed indurated granulomatous lesion closely resembling the human chancre, the other a diffuse infiltration more analogous to the secondary skin lesions of man. Both groups of lesions presented the greatest degree of individual variations and possessed no fixed status but were subject to frequent and marked transformations. After a period of from a few weeks to many months, the lesions in the scrotum disappeared spontaneously.

Local Dissemination, Local Recurrence, and Involvement of Regional Lymphatics. From a study by Brown and Pearce⁵ of the phenomena of the primary infection on the one hand, and the phenomena of local spread, or dissemination, on the other, it is seen that a multiplicity of lesions develops in the testicles and scrotum of the rabbit which have much the same characteristic irrespective of their origin. Some of these lesions are clearly recognizable as primary lesions or parts of a primary reaction to infection; whereas others are just as clearly the results of dissemination of the virus from a primary focus of infection or correspond with lesions which are commonly spoken of as secondary lesions. The effort to draw a sharp line of distinction between these two groups of lesions or between a primary and a secondary stage of infection in the rabbit, however, would be largely an arbitrary procedure. The fact is that the tissues of the scrotum and testicle of the rabbit constitute favorable surroundings for the localization and develop-

(5) Jour. Exper. Med., June, 1920.

ment of *S. pallida* infections. Under ordinary circumstances, a large part of the reaction to infection which expresses itself in the formation of lesions recognizable by ordinary methods of examination takes place in these tissues. These lesions present certain broad and general characteristics without regard to whether they are primary or secondary in origin; the reaction is merely a reaction to a syphilitic infection which in either case may assume the most diverse character.

Further, it would appear that in rabbits infected with such strains of *Spirochaeta pallida* as have been used, the virus is never confined to the area occupied by the so-called primary lesion, or chancre, but always spreads and always gives rise to a regional adenopathy. There may be no lesions to indicate the progress of this dissemination, but an examination of the inguinal nodes shows that dissemination occurs very soon after inoculation, and a reaction may be detected in these glands even before infection can be recognized in the scrotum. Subsequently lesions develop in all parts of the scrotum and testicle, sometimes involving the entire testicle or scrotum, and at others, forming focalized lesions with an especial predilection for certain locations such as the epididymis, the mediastinum testis, the tunica, and the dorsal folds of the scrotum. In some instances, more or less continuous lesions form along the course of the perivascular lymphatics, suggesting that this is one path taken in the dissemination of the organism. It is probable, however, that lesions of a gross character develop more as a result of accumulation of spirochetes than of mere invasion of the lymphatics since they are not a constant accompaniment of the local infection, whereas invasion of the lymphatics and extension of the infection to the regional lymph nodes occur in all cases.

Syphilitic Affections of the Mucous Membranes and Mucocutaneous Borders. In a series of more than 200 rabbits in which generalized lesions were observed by Brown and Pearce⁶ following local inoculation with *Spirochaeta pallida* there were a number of animals in which characteristic lesions were noted on mucous membranes or along mucocutaneous borders. These

(6) Jour. Exper. Med., November, 1920.

lesions were distributed with about equal frequency between the nose or naso-lachrymal system, the eyelids and the genital and anal regions. The lips and buccal mucosa appeared to be less subject to localized infections unless the papillomatous growths noted on the lips and under side of the tongue should prove to be in some way connected with such an infection.

Involvement of the nasal mucosa was very commonly associated with lachrymal overflow and with some degree of conjunctivitis.

The lesions of the eyelids were usually small, elevated papules or lesions of an ulcerative character some of which were surrounded by a zone of infiltration. In exceptional instances, large granulomatous lesions occurred along the margins of the lower lids.

Infection of the penis and sheath gave rise to conditions analogous to those of the nose. In one group of animals, there was a diffuse affection characterized by redness and swelling of the parts with a mucopurulent exudate; in another there were circumscribed or diffuse infiltrations; whereas in a third the lesions formed were indurated granulomatous masses. Secondary necrosis with erosion or ulceration was a common feature of all these conditions.

Localized infections in the region of the anus differed from those in other localities chiefly in the absence of an exudative group of affections and in the frequency with which lesions of a papillomatous type occurred.

Lesions of mucous membranes and mucocutaneous borders developed at periods of time varying from a few weeks to several months after inoculation. Most of them were rather chronic and in several instances persisted in an active condition for considerably more than a year.

Cutaneous Syphilis in the Rabbit. From the study by Brown and Pearce⁷ of a large series of rabbits with pronounced manifestations of generalized syphilis, lesions of the skin and appendages were found to constitute one of the largest and most varied groups of such affections. The conditions noted consisted of alopecias, onychia and paronychia, and lesions of the skin proper.

(7) Jour. Exper. Med., October, 1920.

It was found to be a matter of some difficulty to make a positive diagnosis of syphilitic alopecia, but there were three and possibly four conditions which appeared to be attributable to such an infection. The first of these took the form of a general or local roughening of the coat with falling of the hair which produced the typical moth-eaten appearance associated with syphilitic alopecia in the human subject. A second form of alopecia was essentially an abnormal looseness of the hair which permitted large areas of the body to be completely denuded. The third type of alopecia was associated with definite skin changes, and the hair was readily removable together with an adherent mass of epithelial scales.

Paronychia was comparatively rare but was readily recognized by a characteristic infiltration and exfoliation of the skin about the base of the nails. The incidence of onychia is uncertain. Late in the course of the investigation it was found that alterations in the nails which were not entirely characteristic in themselves might occur in consequence of a syphilitic involvement of the nail beds which could not be detected by ordinary methods of examination. The cases which were recognized as syphilitic were those which showed an associated paronychia.

Lesions of the skin were found to be one of the most frequent manifestations of a generalized infection in the rabbit. These lesions were divided into three classes: first, granulomatous lesions; second, infiltrations, and third, erythemata.

The granulomata were lesions of a fleshy character which tended to grow to a very large size and presented all the characteristics of circumscribed primary lesions of the scrotum.

The conditions described as cutaneous infiltrations included two general types of lesions, one a flattened and rather diffuse process, the other an elevated and sharply circumscribed papule. As a class, these lesions were prone to secondary alterations and in this way gave rise to a great variety of conditions which in general resembled the diffuse primary lesions of the scrotum and the papular lesions resulting from local dissemination.

A third type of lesion resembling the macular ery-

themata of man was observed in a small number of animals, and while no definite proof of the specific origin of these lesions was obtained, the evidence available was strongly suggestive.

In addition, several other cutaneous affections were noted which have not as yet been thoroughly investigated. It is suggested, however, that these processes may bear some relation to infection with *Spirochaeta pallida*.

Clinical Aspects of Cutaneous Syphilis. The purpose of another paper by Brown and Pearce³ of the Rockefeller Institute is to present such facts concerning the occurrence, distribution, and fate of cutaneous lesions as will enable one to formulate a general conception of cutaneous syphilis in relation to other phases of the experimental infection.

From the study of a large number of rabbits with generalized cutaneous syphilis following local inoculation with *Spirochaeta pallida*, lesions were found most often about the hind feet and legs, the head, the front feet and legs, and the tail. There was further evidence of a selective distribution of cutaneous lesions in the fact that, on a given part of the body, the lesions were usually confined to a few restricted areas. About the head, they occurred almost exclusively on the sides and bridge of the nose, the lids, the brows, the lips, and the base and free portions of the ears. They occurred on the front surfaces of the fore-arm, the carpus, and the feet, while on the posterior extremities they were situated upon the dorsum and lateral surfaces of the feet and ankles from the level of the tendo-achillis to the base of the fifth toe. The positions of greatest frequency were the region of the tarsus and external malleolus, the base of the fifth metatarsal, the lateral and posterior surfaces of the heel and tendo achillis, and the base of the fifth toe. In many instances, the positions of predilection were exposed positions or areas of skin covering bony or tendinous prominences.

It was also found that the character of the lesions differed somewhat in the various locations. The lesions of the head were mostly small circumscribed papules or

(8) Jour. Exper. Med., October, 1920.

processes of diffuse infiltration; on the fore-arms and feet, affections of this type were about equally divided with larger granulomatous masses of a chancre-like character, while on the hind feet and legs, granulomatous lesions were far more numerous than those of any other type and frequently reached a very large size.

The cutaneous eruption usually consisted of only a few lesions confined to some one part of the body, but occasionally they were more numerous and more widely distributed. In this connection, it was noted that when multiple lesions appeared in a given area at about the same time, the growth of most of them was abortive, and, as a rule, only one or two developed to any considerable size. Especial emphasis was placed on this phenomenon of inhibition as a factor of fundamental importance in the experimental infection.

From clinical observation, it was found that, as a rule, the first cutaneous eruption occurred at from two to four months after inoculation but might occur either earlier or later, depending upon the circumstances in the individual case. The earliest eruptions appeared three weeks after inoculation and the latest two years and eight months, but, as a rule, the time between inoculation and the appearance of the first eruption did not exceed four to six months.

Successive crops of cutaneous lesions appeared in a number of animals usually within the first six months after inoculation. In a few instances, however, there were repeated eruptions extending over a period of two years or more, the longest recorded period being three years and seven months.

The duration of individual lesions was found to be extremely variable, ranging from a few days in the case of a macular erythema to more than two years in the case of a few granulomatous lesions. The average duration of the lesions appeared to vary somewhat with the nature of the lesion but on the whole was not more than from two to four months. No limits could be fixed, however, for the duration of an active skin infection as a whole.

Again, it was found that the cutaneous infection tended to pursue a periodic or relapsing course. This

was seen in the mode of growth and resolution of individual lesions, the occurrence of successive periods of eruption, and the recurrence of completely healed lesions, all of which was interpreted as evidence of the essential relapsing nature of syphilitic infections.

Syphilitic Infection of the Central Nervous System of the Rabbit. Numerous attempts have been made to devise a means of producing an infection of the central nervous system in a rabbit which might be utilized in studying this phase. The evidence of infection in the experiments hitherto undertaken to demonstrate invasion of the central nervous system has consisted largely in the demonstration of lesions which, although analogous to certain lesions observed in man, might be produced by a variety of causes and are frequently found in rabbits which have not been inoculated with *Spirochaeta pallida*.

Brown and Pearce⁹ have attacked the problem in a different way. They inoculated rabbits with two different strains of *Spirochaeta pallida*, one of which was the Zinsser and Hopkins strain and the other was the Nichols strain. The inoculated animals were eventually killed and the spinal fluid collected without any contamination from the blood or other material. The spinal fluid was then injected into a series of thirteen rabbits. Nine of these rabbits were infected with the Nichols' strain of *Spirochaeta pallida*.

Spirochaeta Pallida in the Cerebrospinal Fluid. An attempt has been made by Arzt and Kerl¹ to determine the infection of the cerebrospinal fluid in various stages of syphilis. By experimentally inoculating rabbits, they determined that it was possible in primary and secondary syphilis to inoculate rabbits with *Spirochaeta pallida*. Inoculations of rabbits with the cerebrospinal fluid of tabetics and other late manifestations of central nervous syphilis were negative.

"Spirochetes" Derived from Red Blood Corpuscles. In studying experimental syphilis in the rabbit, it has been noted on some occasions that testicular fluid obtained by puncture showed in the dark field numerous extremely tenuous, filamentous forms. These flexible

(9) Archiv. Dermat. and Syph., November, 1920.

(1) Dermat. Zeitschr., January, 1920.

bodies in some degree simulated *Spirochaeta pallida* in motility and spiral structure and yet were clearly not the specific organism. Eberson² has made a careful study of these organisms and has been able to demonstrate the transformation of the filamentous forms from red blood cells, particularly when they are placed in normal or slightly below normal salt solution. The bodies bear no relationship whatever to the organism of syphilis and may be produced at will. These non-specific and inanimate bodies may be seen in specimens of fluid that are apparently free from blood. However, a very careful search of numerous fields will reveal the presence of at least one red blood cell which is all that is necessary for the transformation process. The failure to find red cells in a specimen of testicular fluid is not invalidating proof of the contention that the "spirochetes" are thus derived. Both normal as well as spirochete-infected testicles show these bodies, but their presence has nothing whatever to do with the life-cycle of the specific agent in syphilis.

Spirochetes in the Genital Lesions of the Rabbit. In 1914 Kerl and Arzt were able to demonstrate spirochetes which morphologically were identical with *Spirochaeta pallida* in cutaneous erosions of rabbits, particularly about the genitalia and anal region.

During the past year Arzt³ studied in Innsbruck a series of animals suffering from lesions about the genitalia closely resembling those which he had seen in animals in Vienna. He was able to demonstrate the spirochete in both young and adult rabbits. In the adult rabbits he found the percentage of rabbits infected about 31, and in the entire series including the young and old 17 per cent. of the rabbits were infected.

Arzt says that the spirochete was identical morphologically with the *Spirochaeta pallida*. No cultural experiments, however, were carried out and no inoculations were made. The author has not yet determined whether it is actually syphilis of the rabbit which has accidentally been inoculated, or whether it is a spiro-

(2) Archiv. Dermat. and Syph., June, 1920.

(3) Dermat. Zeitschr., February, 1920.

chetal infection of the rabbit by a spirochete which closely resembles *Spirochaeta pallida*.

Latent Infections with the Demonstration of Spirochaeta Pallida in Lymphoid Tissues of the Rabbit. In human syphilis there frequently comes a time during which the patient, although known to be infected, shows no obvious manifestation of an active syphilitic process. Within recent years, more exact clinical methods have shown that some of these patients are the subjects of visceral or of nervous involvement and are, therefore, cases of obscure rather than of latent infection. The work of Warthin has shown further that active pathologic processes may exist where there is no clinical sign to indicate their presence, and finally that spirochetes with more or less tissue alteration may be demonstrated in individuals in whom there is little if any evidence either of disease or of infection.

Brown and Pearce⁴ have been able to demonstrate the evidence of *S. pallida* in lymph nodes of rabbits long after the activity of the infection had apparently subsided.

Six rabbits which had recovered from generalized syphilis were used as the basis for determining whether such animals were still infected and something as to the location of the spirochetes in cases of latent infection.

One of the animals was inoculated four years and three months prior to the examination, another nine months, and the others seven months. At the time the examinations were made, all the animals showed a suggestive adenopathy which was most evident in the popliteal nodes. In addition, two showed slight lesions of an indifferent character in which no spirochetes could be demonstrated by dark-field examination. The others showed no lesions. The latent period of infection was of three months' duration in five of the animals and was six months in the other.

A popliteal node was removed from each of the animals and used for a test inoculation of two normal rabbits. Infection was produced in all cases, the in-

(4) Amer. Jour. Syphilis, January, 1921.

incubation period varying from thirty-one to forty-four days, which is practically the same as that given by lymph-node inoculations during active stages of infection, and shorter than that obtained from blood inoculations except in the most active stages of infections.

From these facts, it may be concluded that rabbits which have recovered from clinical manifestations of syphilis may harbor virulent spirochetes almost indefinitely even though no further manifestations of infection should occur. Moreover, the infectivity of material from the popliteal nodes, taken in conjunction with other evidence of an affinity of spirochetes for lymphoid tissue, is interpreted as indicating that the lymphoid tissues of the body in general are probably the chief reservoirs of the virus during latent periods of syphilitic infection.

CLINICAL MANIFESTATIONS OF SYPHILIS.

The Cause of the Malignant Syndrome in Syphilis.

It has been recently pointed out by Lacapere that arterial hypertension is the cause of visceral lesions in syphilis. The same author⁵ gives some figures which in his opinion point to the localization of the cutaneous lesions due to hypotension. It is a well-known fact that ulcerating and pustular syphilides are very common among the Arabs. He does not believe that this is due to the influence of race, because the Arab race is a mixture of a great many different races, nor does he believe that they are infected by a particularly virulent strain of *Spirochaeta pallida*, because Europeans infected by Arabs have the usual manifestations of the disease.

Among the principal causes of the localization of cutaneous lesions, is, as was pointed out by Fournier, malaria. After traveling about a great deal in Morocco, Algeria, Tunis and other districts the author observed that the cutaneous lesions were most numerous in the malarial districts. In the higher regions, where there was no malaria, he encountered no malignant cutaneous lesions. The rôle played by malaria, in the opinion of this author, is one of lowering the arterial tension.

(5) Bull. soc. franc. de dermat. et de syph., 1920, p. 320.

In studying the blood pressure of 175 native Moroccans he found that it averaged 137 and in twelve natives with malaria it averaged 126. On the other hand, among the Singalese, who are practically never infected with malaria, the average arterial tension was 147.

In addition to malaria, alcoholism plays an undoubted rôle in lowering the arterial tension. Moreover, secondary syphilis likewise is associated with a lowered tension, and all of these taken together lower the resistance of the skin to invasion of the spirochetes.

Treatment with mercury is of very little value in malignant syphilids because it has no action on the arterial tension. On the contrary, arsenical medication leads to rapid improvement because of somewhat increased tension.

In the discussion which followed the presentation of the paper, Queyrat stated his belief that the invasion of the suprarenal with secondary syphilis was the principal factor in the production of the hypotension. This is usually indicated by a white line across the abdomen. He insisted upon making a distinction between *syphilis grave* and *syphilis maligne précoce* which is a more specialized form of syphilis lacking the specific papules and the mucous patches and in which the lesions resist mercury and potassium iodide but yield to arsphenamine.

Malignant Precocious Syphilis. The article of Lacapere quoted above led Queyrat⁶ to give his observations of malignant syphilis in North Africa. In his opinion, suprarenal insufficiency is the rule in primary and secondary syphilis and if one observes closely the white abdominal line will be found associated with hypotension. He also makes a sharp distinction between *syphilis grave* and *syphilis maligne précoce*. The cases of *syphilis grave* are those in which during the course of the secondary period and coincident with the appearance of papules, macules, and mucous patches, there appear lesions of tertiary character and no particular ulceration. In all of these lesions the spirochete can be found.

On the other hand, malignant precocious syphilis is an entirely different manifestation. It begins as a rule,

(6) Bull. soc. franc. de dermat. et de syph., 1920, p. 37.

but not always, with a markedly ulcerated chancre. This is followed by papulo-vesicles which later become pustular, and finally crusted ulcers. This picture had led to a mistake in diagnosis of ulcerating varicella. In this type of syphilis one never sees the roseola, nor do the mucous patches ever occur. The evolution is by successive outbreaks and the old crusted ulcers may be found side by side with recent papulo-vesicles. The different stages of evolution can be easily studied because of the simultaneous existence of the various types. The lesion begins as a small rounded plaque which is dark red. In the center of this erythematous plaque the epidermis becomes elevated and contains a translucent fluid which rapidly becomes secondarily infected, after which the vesico-pustule ruptures and dries into a crust. This is followed by ulceration. On lifting the crust one finds a smooth, well-defined ulcer with an erythematous halo. Simultaneously ulcers may occur in the mouth and nose, leading to perforation, but the mucous patches never develop. Whereas, on the one hand, in *syphilis grave* spirichetes can be found in all the lesions, in *syphilis maligne précocæ* spirichetes can never be found, despite the most careful search.

Another interesting point is that the sero-reaction becomes positive very late, in some cases as late as two or three months after the onset.

The author agrees with Lacapere as to the failure of mercury to exercise any effect on the lesions.

The precocious malignant type runs a fever curve closely resembling that of typhoid, but with very small doses of arsphenamine the curve drops promptly to normal.

Another interesting difference between the two types of the disease is the absence of visceral and nervous lesions in the malignant precocious type.

Syphilis of the Liver. An excellent review of the literature and a description of the various manifestations of syphilis of the viscera is made by U. J. Wile,⁷ in a series of articles. The nature and length of the articles make them unsuited for use in these volumes but the reader who is interested in the subject of syphilis of the

(7) Archiv. Dermat. and Syph., 1920.

viscera is urged to read the original articles. The author does not enter into the controversy which is waging so animatedly in Europe at the present time as to whether icterus is due to syphilis or to arsphenamine.

Preroseolic Syphilitic Periostitis. Observation of the case of a child 18 months old who developed a periostitis a few weeks after the development of a chancre led Chastellier⁸ to record his case and to report a study of the literature.

One of the earliest cases recorded was that of Bell in 1802 who wrote: "I have seen the bones affected, even at the time when there was no reason to suspect that the virus had penetrated the system."

Age and sex seem to have no influence in the process of the development of these bone lesions. Men are more commonly affected but that probably is because early syphilis is more common among men. As a rule, these lesions occur in young and robust individuals. Usually the first symptom of the lesion is an intense pain of a neuralgic type. Very soon a swelling appears and the pains increase. The patient is unable to stand the least amount of pressure. The pains, as a rule, are worse at night and this is of considerable value in diagnosis. The prognosis is excellent for, as a rule, these lesions heal even in the absence of treatment. No attempt is made to explain the precocious localization of bone lesions.

Syphilis in Tunis. During the years 1917, 1918 and 1919, Jamin⁹ had charge of the treatment of syphilis among the recruits in Tunis.

The object of the treatment among the recruits was to render them temporarily fit for duty by removing all evidence of active lesions. Of the 701 men who were given what is known as the treatment of "*blanchiment*," 94.15 per cent. remained free from lesions for varying periods of time and forty-one of this number, or 5.8 per cent. were greatly improved. Forty of these cases, however, or 1.4 per cent., remained without benefit.

The author gives many interesting observations concerning the character of the lesions present in these Arabs and the reason therefore. The cutaneous lesions

(8) Ann. de dermat. et de syph., October, 1920.

(9) Ann. des mal. vén., September, 1920.

are very common and are of the ulcerating gummatous type. Practically all of the patients are secondarily infected because of the water supply. The Arabs are much given to ablutions but the water used in the ablutions is practically always infected with a great many different kinds of organisms. Owing to the contact of the individual with various other members of the family in his daily life, acquired syphilis is found at a very early age among the Arabs. The result is that late tertiary lesions are common in early adult life. Mucous membrane lesions are probably the most commonly observed type of recurrent lesions. Bone and visceral lesions were very rare as were also cases of hereditary syphilis. No case of central nervous system infection was found among all these recruits.

Syphilis Among the Israelites in Morocco. The work of Decrop and Salle¹ in the syphilitic clinic at Fez is of interest from the statistical point of view and particularly because it shows the comparative rarity of syphilis among Israelites. The better the class of Arabs, the less frequently was syphilis encountered, as was shown by Lacapere in 1917. In a series of 4,000 observations since the creation of the dispensary in 1916, the authors had observed only 141 cases of syphilis among Israelites. The extragenital chancres were much more numerous than the genital chancres, which indicates that syphilis among these people, as it is among the Arabs, is contagious rather than venereal.

The lesions of the secondary period in the Israelites resembled those occurring in the European much more closely than those occurring in the Arab. There were many more mucous membrane lesions than cutaneous lesions and the visceral lesions were much less frequent. Only one case of headache was encountered. About one-third of the cases were of the tertiary period.

Also it is of interest to note that the Israelites with latent syphilis, and particularly the pregnant females presented themselves for serologic examination and treatment quite frequently, which is rarely the case among the Arabs. The life of the Arab is quite different from that of the Jew. The former crowd together in

(1) *Ann. des mal. vén.*, March, 1920.

great numbers in very small houses, between which the streets are extremely narrow, and obviously syphilis in one member of a family of ten or fifteen persons is quickly passed on to the other members. The Jews, on the other hand, are isolated from the Arab population and excluded from certain regions. Moreover, they are obliged to wear a conspicuous and characteristic costume and under no circumstances could an Arab be induced to have intercourse with a Jewess. The Jews live grouped about their conservative rabbis and conform to their religious rules. The system of child marriage whereby girls of six and seven and boys of twelve and thirteen years are married, leaves no place for prostitution, which is strictly forbidden and severely punished. Clandestine prostitution is practically impossible in domestic life where every movement of one individual is known to all the others. In 1910, shortly after the arrival of the French, a woman who gave herself up to prostitution was killed by the enraged population. Since the arrival of the French the restriction of the movements of the Jews have been removed and prostitution is increasing.

Unusual Manifestations of Syphilis. Two cases of unusual manifestations of syphilis are reported by Linne-man.² One case was a gummatous invasion of the bladder wall resulting in dysuria which led to an erroneous diagnosis of gonorrhea. The cystoscopic examination revealed a sharply margined growth in the bladder wall. The positive Wasserman reaction and the prompt relief after the institution of antisyphilitic treatment was conclusive of the diagnosis of gumma of the bladder.

The other case was an urticaria-like eruption in a patient who had syphilis. Over the back, chest, neck and arms, as well as on the legs, were patches varying in size from one to eight inches in diameter, in places raised one-eighth inch above the normal surface, and sharply margined. In the center of most of the patches there were thin scales. Raw spots developed, particularly at points of rubbing or irritation, in the region of the buttocks and neck especially. The itching and burning were severe. Besides these large lesions, there were a few smaller squamous lesions here and there

(2) *Archiv. Dermat. and Syph.*, July, 1920.

and some discoid patches on the forehead. It was noted that some of the urticaria-like lesions, even in the large raw places, disappeared in twenty-four hours, and new ones elsewhere reappeared. Pigmentation was prone to develop early in those that showed healing. The treatment consisted of intravenous injections of arsphenamine, after which the itching slowly disappeared in the course of two weeks.

SYPHILIS ASSOCIATED WITH OTHER SKIN LESIONS.

Nevus Verrucosa in a Hereditary Syphilitic Cured by Mercury. The question of the rôle which syphilis may play in the development of nevi is brought up by an observation made by Gougerot and Dessaux.³

The patient was a girl, 12 years old, who had a verrucous linear nevus on the dorsal surface of the hand which had been present since birth. On the palm were numerous small verrucous lesions of recent development and on the face there was a stellate angioma. In two previous communications, Gougerot has called attention to the co-existence of hereditary syphilis and verrucous nevi; therefore, when this case came under his observation, he made an intensive examination for syphilis. The Wassermann reaction was strongly positive and there were also present a number of stigmata of hereditary syphilis. After a series of calomel injections, the lesions entirely disappeared.

In Gougerot's opinion, hereditary syphilis plays a very important part in the development of nevi. The rôle played by the syphilis in the predisposition for dystrophies is not understood but the fact remains the same. He insists that in all cases of a similar type a careful examination should be made for syphilis and especially the Wassermann reaction should be done. In case of positive findings, immediate and energetic treatment should be instituted and in such cases the prognosis for cure is excellent.

The So-Called Anorectal Syphilome of Fournier. In 1875, Fournier described under the name of "*syphilome*

(3) Ann. des mal. vén., October, 1920.

anorectal" an affection which is very rare and is highly characteristic, occurring about the rectum and the anus. This affection consists of a hyperplastic infiltration of the anorectal walls and ends in a retraction of the rectum. It is extremely chronic and develops during a number of years and in some cases without the patient being aware of it. Ordinarily the stage of infiltration passes unnoticed and it is not until the retraction of the rectum occurs that the patient is aware of the disorder.

A study of six cases of this disorder has recently been made by Jersilde.⁶

According to Fournier there are four characteristics of this anorectal syphilome.

First, a peri-anal infiltration which is divided by the anal folds and withdrawing of the sphincter in globulated tumors: These tumors are covered by the normal mucosa or by intact skin. The tumors are hard and elastic. If they become inflamed or develop into ulcerations, they may become decidedly painful.

Second, a rectal infiltration: When the finger is introduced into the rectum, one is able to perceive instead of the usual cylinder of soft wall, a ridged tube with thickened walls. The infiltration occupies exclusively the lower portion or the ampullary portion of the rectum and extends upward for a height which rarely exceeds 8 cm., and around the entire circumference of the bowel. The mucosa, as a rule, is not cicatrized nor ulcerated. The peri-anal infiltration is, as a rule, contiguous with the rectal infiltration. Occasionally the two lesions are separated by an intermediate zone of normal tissue.

Third, retraction eventually occurs in the rectal region and is always within easy reach of the finger. Ordinarily it commences in the anus and occasionally it is not quite so high up. As yet the retraction has never been known to occur out of reach of the examining finger. Retraction may be irregular and may occupy only a section of the circumference, or it may be regular and extend entirely around the intestines, in a band several centimeters in width. The retraction is always fibrous.

In addition to these three characteristics, occasionally there is added a fourth, namely fistula. These fistulae

(6) Ann. de dermat. et de syph., February, 1920.

are frequently multiple with their external orifices in the region of the anus and are situated in the walls of the rectum. Fournier mentions the existence of the fistulae but he does not seem to attach very much importance to their presence.

All six of the cases observed by Jersilde occurred in women. This is in accordance with the observations of other men who report a proportion varying from one to eight. The age of the women ranged from 25 to 32 years and the duration of the disease was from three to nine years.

The symptom most commonly observed by the patient was a modification of the caliber of the feces. It was reported that they observed a diminution of the size of the stool varying from that of a pencil to that of a finger. All the patients had a rather decided loss of sphincter control.

That syphilis played no rôle in the development of some of these cases was proved beyond doubt. In one of the patients, a woman 27 years old, had had the disorder for a period of seven years yet when she entered the hospital she presented a well-developed and characteristic secondary roseola of syphilis. The patient had two children, five and six years of age respectively, both of whom were well-nourished and free from syphilis. Another patient who first was seen in 1913 and treated for the so-called syphiloma, developed syphilis in 1917.

Moreover, in one case it was demonstrated that the patient never had had syphilis and in two of the cases, it was demonstrated that the patient had contracted syphilis four and eight years respectively before developing the so-called anorectal syphiloma.

Inasmuch as the authors and others have observed the co-existence of vulvar elephantiasis, he is of the opinion that the process of this syphiloma is that of elephantiasis.

The pathogenic mechanism is probably as follows:

First, a lesion (chancre, chancroid, wound) of the peri-anal region with adenolymphangitis of the inguinal group. Arrest of the lymphatic circulation in the glands of the inguinal region or in the afferent lymphatic vessels of these groups.

Second, diverting the lymph of the genital region by the rectal lymphatics toward the glands of the rectum.

Third, anorectal adenitis with posterior obliteration.

Fourth, lymphatic spaces between the two obliterations resulting in rectal infiltration or peri-anal infiltration depending on the seat of the obliteration.

Juxta-Articular Nodes and Syphilis. Nodules occurring about the articulations, especially of the hands, have been observed in natives of the tropics by many different men and have been observed particularly by Jeanselme, who has given them the name "juxta-articular nodes." Gougerot believes these are due to a fungus which he calls "*Nocardia carougei*." Others have ascribed the etiology to tuberculosis and still others to filariasis. In 1919, the occurrence of the nodes in leprosy was described by Currie and Hollman.⁷

Burnier and Bonnin⁸ now give an interesting account of the occurrence of these nodes in a patient with syphilis.

Careful histologic and bacteriologic examinations were made to determine if these corresponded to the juxta-articular nodes described in the tropics. The patient had been in the tropics some ten years previous to coming under observation, and had been in France during the *interim* so that there was some doubt cast upon the possibility of these nodes being of the type described in the tropics because of the long absence from the tropics. Histologically, however, they corresponded to the nodes described as occurring in the tropical regions. The bacteriologic examination was negative for the fungus described by Gougerot in his original communication. Therapeutically, the lesion yielded almost completely to antisypilitic injections. If the lesion is not a juxta-articular node, the authors are inclined to believe that, at least clinically, it is a subcutaneous sarcoid with a tendency to occur about the articulations. In their opinion every patient presenting a juxta-articular node should have a thorough examination for syphilis before this diagnosis is rejected.

Syphilis and Pruriginous Dermatoses. In dermatol-

(7) Practical Medicine Series, 1919, Vol. VII, p. 43.

(8) Ann. des mal. vén., May, 1920.

ogy it is almost axiomatic that a syphilitic lesion never itches. Leredde has in the past two years published a number of articles in which he adduces some evidence in support of his conviction that many diverse dermatoses hitherto thought unconnected in any way with syphilis, are of syphilitic origin. He⁹ now reports in detail sixteen cases, consisting of various types of eczema and one case of lichen planus. Of the sixteen patients there were four who gave a history of syphilitic antecedents and one in whom there was a positive Wassermann reaction. The treatment consisted in local applications and injections of arsphenamine or mercury. Some of the cases made a partial recovery; others only a temporary recovery with recurrences.

[Eczema and syphilis are two very common disorders and merely because they happen to co-exist in an occasional patient is no reason for supposing that syphilis is the cause of the eczema. One might argue with just as much basis in fact that syphilis was caused by the eczema. In these cases, however, there was no evidence of syphilis but merely "syphilitic antecedents." Moreover, there was nothing whatsoever that was striking in the therapeutic results for which local application and general care could not easily account. Fournier was accused by his contemporaries of seeing syphilis everywhere. Leredde might be accused of being able to see nothing but syphilis.—M.]

Urticaria Probably Due to Syphilis. Two cases of urticaria which were probably due to syphilis are reported by Hollander,¹ because he believes that the present literature contains no reports of pruriginous lesions being attributed to syphilis.

The first patient was a girl aged 5 years who had urticaria which was produced by currents of air for the past three years. There was a fairly definite history of syphilis in the mother which led to the taking of blood for a Wassermann reaction which was found to be positive. The patient was put upon mercurial treatment and about two months after instituting treatment, the symptoms disappeared.

(9) *Ann. des mal. vén.*, December, 1920.

(1) *Archiv. Dermat. and Syph.*, January, 1920.

The other patient was a man 38 years old, who had urticaria which had been present for seven years. He had a definite history of a chancre and a strongly positive Wassermann reaction. He was given ten injections of 0.6 gm. of arsphenamine and after four weeks of treatment, the urticarial symptoms disappeared.

[The author has evidently overlooked the observations of Hazen which were published in the *American Journal of Syphilis*, for October, 1917. In that report Hazen stated that he had found twenty-eight cases of urticaria in his dispensary practice with positive Wassermans. Most of these cases cleared with either the use of mercury or of arsphenamine. Hollander is also referred to the work of Milian, Leredde and others.—M.]

Urticaria and Syphilis. Several years ago, Hazen called attention to the fact that in the dispensary class of patients urticaria was not infrequently of syphilitic origin. In his cases all the patients had a positive Wassermann and all of them yielded promptly to arsphenamine injections.

Leredde² reports in detail two cases in which there was itching dermatosis probably of syphilitic origin. In one case the disorder had been present for four years. It did not yield, however, to arsphenamine injections until the thirteenth injection had been given which is quite contrary to the experience of Stevens. The other case occurred in a patient aged 60, and even after a still larger series of injections, the disorder had not entirely cleared up.

[The two cases reported by Leredde are not at all convincing. We have in our own work encountered patients who had chronic urticaria and a positive Wassermann. The urticaria promptly disappeared after one small injection. It then occurred to us that probably it was due not entirely to the arsphenamine but to the alkali contained in the arsphenamine solution. We found that by injection of Fischer's solution the results were comparable to those of arsphenamine. Likewise in non-syphilitic cases, there was decided improvement after the administration of Fischer's or other alkali solutions. This would be in accordance with the ideas of

(2) Bull. soc. franc. de dermat. et de syph., 1920, p. 171.

Fischer who believes that many cases of edema and urticaria are probably due to acidosis.—M.]

Polymorphous Eruption Due to Serum Therapy and Syphilis. An unusual sequence of events was observed by Gaston³ in a patient who had had a penile chancre three months before coming under observation. The chancre healed without manifestations other than adenopathy. Later the man contracted scabies and diphtheria. He was given antidiphtheritic serum in large doses. Within a week after the injection of the serum there was an eruption of papulo-squamous syphilides over the entire body. Simultaneously there appeared a multiform erythema. There was no particular systemic disturbance and the urine was normal. The case was interesting because of the presence of the erythema multiforme due to the serum injections and because of the sudden development of a papular syphiloderm which had hitherto failed to develop. In Gaston's opinion, the antidiphtheritic serum led to the production of a secondary eruption which previously had passed unnoticed.

Diabetes and Syphilis. Syphilis as an antecedent of diabetes mellitus has been noted for years. The work of Warthin a few years ago attracted much attention and has again aroused interest in syphilis as an etiologic factor in diabetes. Two interesting cases in which diabetes and syphilis were closely associated, one probably following the other, are reported by Cordier and Dechaume.⁴

In order that a case of diabetes may be considered as syphilitic in origin it must fulfill the following requirements:

First, the appearance of the diabetes must follow the syphilitic infection.

Second, it must appear at the same time as other syphilitic manifestations.

Third, the mercurial treatment must cure simultaneously the syphilitic lesions and the diabetes.

Fourth, the antidiabetic treatment must have no effect on the diabetes.

It was admitted by the patient that he had received

(3) Bull. soc. franc. de dermat. et de syph., 1920, p. 11.

(4) Ann. de dermat. et de syph., January, 1920.

treatment at the time of infection. Tertiary cutaneous lesions were present and yielded to the mercurial treatment. In the second case the syphilitic infection had not been discovered. In this case there was leukoplakia of the mucous membrane of the mouth. Inequality of the pupils and osteitis were observed. The Wassermann reaction was strongly positive. In both cases there was definite diabetes and not a temporary glycosuria.

Buccal Leukoplakia Among the Syphilitics in Algiers. There are two types of leukoplakia which, topographically at least, are known, namely the triangular, which occurs at the commissure and is known as the mucous patch and the lingual keratosis. Fournier was of the opinion that this triangular patch occurring at the commissure was not of syphilitic origin.

Montpellier⁵ in North Africa found twenty-four cases of leukoplakia among 100 syphilitics with active syphilis. Inasmuch as the natives are great smokers and are very fond of spiced foods, the author raises the question as to whether these have been a factor in the production of the leukokeratoses. However, the recent statistics of Raillet were practically those of Montpellier and occurred in natives of Europe. The great difficulty in the way of determining the rôle played by syphilis in leukoplakia is the fact that it is impossible in all cases with our present methods of examination to determine whether or not the patient is free from syphilis. Bonnet, in 1917, made an attempt to determine this by a study of leukoplakia occurring in patients who had recently become infected with syphilis. Therefore, in those cases the recent syphilis could have played no rôle in the production of the leukoplakia.

A number of authors, Milian in particular, are of the belief that leukoplakia, both lingual and buccal, are manifestations of a special type of syphilitic virus. They believe that not only is it due to a special strain of *Spirochaeta pallida* having a particular tissue affinity, but also to a strain having a sclerosing rather than a destructive action on the tissue. Leukoplakia, in their opinion, is the result of the action of the neurotropic and not the dermatropic strain.

(5) Ann. des mal. vén., November, 1920.

Of the twenty-four patients with leukoplakia, there were eighteen who had entered the hospital for cutaneous or mucous lesions. Among these there were four mucous patches of the buccal mucous membrane or genitalia and ten cutaneous gummas, some of which had rather deep and mutilating ulcerations; one case of severe arthritis; two of osteoperiostitis; and one case of severe phagedenic ulceration of the face.

Consideration of these figures would lead one to believe that leukoplakia rather than being a manifestation of the action of the neurotropic strain is the result of the dermatropic strain. The frequency of leukoplakia and the rarity of nervous syphilis among the Algerians would argue convincingly against the dual theory of the syphilitic virus.

Syphilis and Cancer of the Buccal Mucosa. The frequency with which cancer of the buccal mucosa is found associated with syphilis has led Cary⁶ to make a careful study of 907 case histories which were found chiefly in the files of Johns Hopkins Hospital, for the purpose of determining the frequency with which syphilis is an associated disorder in cancer occurring about the mouth, especially the tongue. The author found that syphilis in association with cancer of the tongue was three times more common than in association with cancer in other locations about the mouth; the percentage was 14.5 or about one in seven cases. The author urges immediate treatment of the lesion as cancerous and not as syphilitic because he feels that valuable time is lost in treating the lesion with antisymphilitic medication.

The Value of the Tubercle of Carabelli as a Sign of Hereditary Syphilis. The dental stigmata of hereditary syphilis are well known and are of great diagnostic value but not all are agreed as to the value of the tubercle of Carabelli. Sabouraud attaches the greatest importance to this sign, where as Jeanselme, Mozer and Chenet believe it has little if any value. Pinard⁷ has made a careful study of the value of this tubercle in a large number of cases. He reports in detail a large series in which the tubercle was present and undoubted signs of syphilis

(6) Jour. Amer. Med. Ass'n., Sept. 25, 1920.

(7) Bull. soc. franc. de dermat. et de syph., 1920, p. 218.

were present either in the patient or in his ancestors. Pinard believes that it is of great value in diagnosis but very little value in prognosis. A patient may never have any trouble, may be entirely free from active syphilis and his intelligence may be of normal or even above normal quality.

CONGENITAL SYPHILIS.

The Pathology of Congenital Syphilis. A careful study of the body and the tissue of a fetus of 7 months development born of a mother who gave a history of perfect health and no evidence of syphilis other than a positive Wassermann, was made by Frazer.⁸ The child, who died shortly after delivery, had at the time of birth a rose-colored macular eruption on the skin of the limbs and trunk and bullous lesions and denuded areas (the remains of ruptured bullae) on the soles, palms, wrists and fingers. A few of these bullous lesions could still be seen in the preserved specimen, but the macular eruption disappeared, as most skin lesions do, shortly after death.

The author goes into the various theories concerning the probable *modus operandi* of the infection of the fetus. From a review of the antenatal pathology and embryology and the morphologic evidence in this case, as indeed in all cases of congenital syphilis, Frazer believes that the infection takes place only after the fetal organs have been formed, a fact which excludes the theory of germinal transmission unless we assume a practically unsupported theory of "larval inactivity" of the infecting organism. From the facts reviewed the most plausible explanation of the 5 per cent. residue of non-syphilitic and immune mothers of syphilitic children is that these mothers have a mild, low grade form of syphilis.

Acquired Syphilis in the Congenital Syphilitic. After the observation of three cases, Goubeau⁹ believes that acquired syphilis in the congenital syphilitic is characterized in a number of ways by some rather striking fea-

(8) *Archiv. Dermat. and Syph.*, May, 1920.

(9) *Bull. soc. franc. de dermat. et de syph.*, 1920, p. 107.

tures. He says that the incubation period is greatly lengthened and may even extend to sixty days. The chancre in itself is of very great import and frequently is phagedenic in character. The precocity and the intensity and the multiplicity of the secondary reaction are decidedly grave. Moreover, the tendency for very early involvement of the central nervous system is marked. Tertiary lesions in general occur very early. The treatment must be very energetic and persevered in.

In the discussion which followed the presentation of this paper, Pinard took decided issue with the author. He stated that experimentally it had been shown that inoculation of syphilitics with *Spirochaeta pallida* resulted in a chancre of very short incubation period and in a chancre which was decidedly mild in its appearance and size. The incubation period might be reduced even to twelve days. In his experience, acquired syphilis in congenital syphilitics ran a very mild course. Gougerot was of the same opinion as Pinard. In his experience acquired syphilis in the congenital syphilitic ran a very much attenuated course.

[It is illogical to suppose that a congenital syphilitic would, upon acquiring new infection, be more susceptible and have less resistance than one who was acquiring syphilis for the first time. This is in accordance with the observations of many men among aboriginal people. When syphilis is first introduced among the aborigines, it is particularly fatal, as has been shown in the South Sea islands and among the Eskimos. Theoretically, at least, syphilis might become so wide-spread among a given people with consequent immunization that eventually the infection would be of a very mild character.—M.]

TEACHING OF SYPHILIS.

The Vanishing Lesion: A New Problem in Teaching. The disappearing of cutaneous syphilitic lesions confronts us with a new problem says C. Morton Smith.¹ The teacher of clinical syphilis must regard this changing condition with real apprehension. One no longer

(1) *Archiv. Dermat. and Syph.*, November, 1920.

sees in the clinic the array of active lesions, both early and late, that were formerly available for teaching purposes. This condition is due largely to four causes: (1) early diagnosis; (2) better treatment, especially with arsphenamine; (3) prohibition, and (4) education.

Without the presence of infectious lesions it is difficult to teach the physicians and nurses in the public health courses. Syphilis, therefore, appears to them a benign infection. Practically the only lesions that are now available for demonstration are the ones new patients and occasional ward patients may show. The lack of material is especially felt in the work with the dental students, in whose instruction lesions in the mouth and throat, or about the face, are especially desired. One can not assume the responsibility of the danger of contagion to associates by withholding arsphenamine from patients with infectious cases; and if arsphenamine is given, the desired patches are promptly healed. It seems highly probable that the whole plan of teaching syphilis, especially of the early infectious lesions may have to be changed, perhaps transferred from the out-patients to the ward, relying no more on ambulatory patients but carrying out bedside instruction. At present, there are about thirty beds available for infectious syphilitic patients in all the Boston hospitals combined, and throughout the state a large majority of the hospitals, both public and private, are still closed to syphilitic patients, either by custom, prejudice or the articles of incorporation.

From the therapeutic standpoint, the vanishing lesion is most encouraging, but to those who feel that syphilis is still a disease that should be diagnosed by the clinical signs and checked up by the laboratory, rather than left entirely for its diagnosis to the serologist, the outlook is not reassuring.

With the decreasing opportunities for observing primary lesions and the early syphilides, the medical profession as a whole will become still less acute in recognizing syphilis, especially the extragenital infections situated in unusual places. Within a year, Smith has seen three cases in which the primary sore was excised by a competent surgeon for a supposed malignant growth of

the cheek, lip and tongue. If competent surgeons are doing such things, how many more cases are being unrecognized by the members of the profession who, for one reason or another, are less well trained? It is common knowledge that most of the primary lesions on the hands or fingers are found in those who care for the sick; yet, knowing this, what is so rare as the early diagnosis of a doctor's digital chancre? These cases are always maltreated by deep incisions, curetting and poulticings; and the diagnosis is often made only when a secondary eruption presents itself, or a positive blood Wassermann reaction is obtained. Often from three to six months have elapsed since the infection occurred, during which time the wife usually has contracted the disease. Probably more chancres of the tonsils have been removed without recognition than all other extragenital primary chancres combined. Moreover, many of the patients were operated on with the secondary rash showing, and often the immediate object of the tonsillectomy was to relieve the acute painless swelling of the tonsil gland.

During the war many civil conditions were temporarily given a military rating; and syphilis was once more brought into prominence as a venereal disease. With such a classification in the army and the navy, there can be no just criticism; but to class all marital, congenital and extragenital syphilis of civilians as a venereal disease is unfortunate and unfair. Smith urges a concerted action on the part of the medical profession to overcome the renewed impression that syphilis and venereal disease are synonyms—in other words, that sin and syphilis are always inseparable. During the past year, the author has seen an unusual number of undoubted early secondary syphilitic patients in whom the site of infection could not be determined in any way, and there was absolutely no glandular enlargement or remains of a possible chancre. Is this to be a frequent occurrence of the future? Is the primary lesion also vanishing?

Suggestions as to means of overcoming the difficulties outlined in Smith's paper are as follows:

Provision of sufficient beds to care for the acutely

infected individuals who can not be properly isolated at home.

Segregation of syphilitic patients into one department, in which the various phases of the disease can be studied and treated.

Collecting photographs of all lesions that can be shown by prints or lantern slides is urged.

Applying (if possible) the color process of photography and the creation of wax models or moulages which are utilized to such a great extent in European medical schools.

MARRIAGE OF SYPHILITICS.

Report of a Commission for the Study of the Question of the Marriage of Syphilitics. On the suggestion of Brocq, the *Société française de dermatologie et de syphiligraphie* appointed a commission to study the marriage of syphilitics. This commission was composed of Queyrat, Hudelo, Spillmann, Gaston and Simon. Each one of the members wrote a report which was discussed in general. Finally a report on which all of the men agreed was submitted to the society.⁷

The syphilitic who marries takes the following chances:

First, contamination of the wife or husband.

Second, transmission of syphilis to the children.

Third, bringing to the *ménage* an altered health which may markedly diminish the social value of the individual; syphilis may shorten the longevity and may lead to visceral and, especially to nervous complications.

With the present methods of treatment, the risks of contagion are very slight because the lesions are promptly cured and rarely recur. The members of the commission are agreed that with sufficient treatment the possibilities of contagion after the first year are very slight. The possibilities of a conceptional contagion, however, are quite different. They were not agreed on this point. The possibilities of contamination of the wife through the semen are well known. The work of Finger and Landsteiner are recalled and in that work those men were able to get positive results with the spermatic fluid

(7) Bull. soc. franc. de dermat. et de syph., 1920, p. 233.

in two cases. In one case the donor had testicular lesions; in the second the testicles were clinically unchanged. Uhlenluth and Mulzer also obtained positive results. Finally, *Spirochaeta pallida* has been found in the spermatic fluid, especially by Pinard. It is difficult to comprehend how an organism so large as *Spirochaeta pallida* would infect the spermatozoön. It is possible, however, that a sporulating form, which would of necessity be very small, might invade the spermatozoön. Many syphilographers, of which the number is constantly increasing, deny the possibility of the mother being infected by the fetus. They insist that every woman giving birth to a syphilitic infant has been infected prior to the conception. The fact that the chancre has not been seen proves nothing. The benign character of syphilis of the so-called conceptional type may be explained by attenuation of the virus gained in the husband under the influence of treatment and of time.

The possibility of paternal heredity has been reduced to a minimum under modern therapy. Every syphilographer, however, has seen cases in which a patient armed with all the possible medical certificates of cure has married and has had syphilitic children. Moreover it is a well-recognized fact that an old syphilitic without contaminating his wife, may have offspring with various dystrophies, although the offspring may not have active syphilis. The dystrophies might be due conceivably to a toxic action on the spermatozoa by the spirochetes in the father.

Maternal heredity is of a much graver nature than paternal heredity. Every woman who has contracted syphilis prior to conception and who has active lesions will invariably give birth to a syphilitic infant. Moreover, a woman who has an old syphilis which appears to be entirely inactive and who has had no signs for years may give birth to a syphilitic infant. In the opinion of the commission, the question of the marriage of the female is a much graver one than the marriage of the male. This is a point which has not been brought out with sufficient clearness by the various authors. Practically all the authors have much to say about the husband but little or nothing about the wife.

The commission lays down a few rules which may serve as a guide to those who contemplate advising their patients concerning marriage.

First, if the patient has been seen and treated during the primary period before the appearance of the serologic and secondary reaction, and the patient remains free from positive serologic and secondary manifestations during the first year, at the end of two years the individual may safely be allowed to marry.

Second, if the patient is seen and treated after the appearance of the serologic reaction or even after the appearance of the secondary symptoms and is given intensive treatment during the period of two years, and if the serologic reactions, the urine reaction, and the reactivation tests are negative, and the spinal fluid is normal, one may safely at the end of two years allow this patient to marry.

Third, if the seroreaction is persistently positive in the blood and the spinal fluid is normal, what is one to do? Would it be possible to continue this treatment until the blood becomes negative, or should one allow the patient to marry? In the opinion of the commission, a persistently positive Wassermann reaction should not necessarily prevent the patient from marrying provided two conditions are fulfilled: first, that the spinal fluid is negative and, second, that the patient is a man. It is well known that men with persistently positive Wassermanns have married and have had perfectly normal, healthy children.

Fourth, if, in spite of the energetic treatment, the blood reaction is either positive or negative, if the spinal fluid is positive, one must be very careful about advising marriage. If, after energetic treatment, the spinal fluid becomes negative and remains negative for a few years, one would be safe in permitting the candidate to marry.

Fifth, if the patient presents positive signs of involvement of the nervous system, one must absolutely insist that the patient shall not marry.

Sixth, if the patient, an old syphilitic, is unable to give a definite and clear account of his infection and of his previous treatment, one must be very cautious about

giving him an opinion and, unfortunately, this is perhaps the most frequent situation in which the syphilographer finds himself.

SEROLOGIC TESTS.

Sachs-Georgi Reaction. In a series of 800 sera, Keining⁸ found that the reaction agreed with the Wassermann reaction in 94.8 per cent. In no case was there a non-specific reaction. In seven cases of primary lesions the Wassermann reaction was positive, whereas the Sachs-Georgi reaction was negative. In sixteen cases the Sachs-Georgi reaction was definitely positive whereas the Wassermann reaction was negative. The reaction remained positive much longer than the Wassermann and is much less influenced by arsphenamine and mercurial treatment. In tuberculosis and acute exanthemata the Sachs-Georgi reaction was negative.

Modification of the Sachs-Georgi Precipitation Test. Because of the large volume of reagents used in the Sachs-Georgi test, the rather scant precipitate often formed, and the length of time elapsing before the test is read, Hull and Faught⁹ have devised a modification which is much easier to manipulate and is no less sensitive than the test performed in the usual way.

The antigen is diluted very carefully with constant shaking. The required amount of undiluted antigen is placed in an Erlenmeyer flask and sodium chloride solution is added drop by drop by vigorous shaking until at least 5 c.c. of the diluent has been run in. The sodium chloride solution can then be added more rapidly, but the vigorous shaking should be continued. The resulting suspension should be very turbid and milky. The antigen should be roughly titrated so that the optimum amount of precipitation will be obtained. To accomplish this the antigen is diluted 1:10, 1:20, 1:40, 1:60, 1:80. Of each of these diluents 0.1 c.c. is then added to 0.3 c.c. of a known positive serum. The dilution giving the optimum result should be used in the test.

(8) Dermat. Zeitschr., 1920.

(9) Jour. Immunology, November, 1920.

The serum should be clear, but it does not matter whether it has been inactivated or not. After setting up the test the tubes may be allowed to stand over night, or centrifuged and read immediately.

The optimum results are obtained by low temperatures for incubation. Room temperature or ice-box temperature has been used in these tests. In setting up the test, to each tube is added 0.3 c.c. of clear serum and 0.1 c.c. of antigen properly diluted. The tubes are then shaken and either centrifuged and read immediately, or allowed to stand over night in the ice-box.

The Sachs-Georgi test agreed with the Wassermann test in 88 per cent. of 296 sera; in 7 per cent. it was more delicate, giving positive results in sera in which the Wassermann test was negative; in 5 per cent. it was negative when the Wassermann test was doubtful; in 2 per cent. it was negative when the Wassermann test was positive.

Treatment of the patient apparently affects the results of the precipitation, causing it at times to become negative whereas the Wassermann test remains positive.

Optimum Conditions for Carrying Out the Sachs-Georgi Reaction. The optimum conditions for carrying out the Sachs-Georgi reaction have been determined by Poehlmann.¹

The reaction was carried out at various temperatures. The ordinary temperature of 37° C. for two hours and then allowing it to stand at room temperature was found to give weaker results than allowing it to stand for twenty-four hours at room temperature. A preliminary stay of two hours in the ice-box was found to increase somewhat the precipitate over the ordinary method of two hours in the incubator. Increasing the percentage of the salt solution above 1 per cent. lessened the reaction very decidedly and over 2 per cent., it minimized it. Inactivation of the serum for carrying out this test is not necessary but the author finds that inactivation for one-half hour gives better precipitation than the inactivation for five minutes as recommended by Georgi. Allowing this serum to stand for from forty-eight to fifty-two hours after drawing the blood was found to give

(1) *Dermat. Zeitschr.*, January, 1920.

better results than carrying out the test immediately after separation of the serum.

Influence of Temperature and Duration of Primary Incubation Upon Anticomplementary Activity. Continuing their valuable researches on the standardization of the Wassermann reaction, Kolmer and Trist² have found that temperatures of from 37° to 38° C. particularly increase the non-specific fixation or inactivation of complement by organ extracts or antigens and sera, commonly designated as the anticomplementary activity of these substances.

Temperatures of from 8° to 10° C. for four hours have no appreciable influence upon increasing the non-specific fixation or inactivation of complement by various antigens.

Temperatures of from 8° to 10° C. for eighteen hours greatly increase the anticomplementary activities of cholesterolized extracts and to a lesser extent of extracts of acetone-insoluble lipoids; there is less effect upon the anticomplementary activity of plain alcoholic extracts.

Temperatures of from 8° to 10° C. for four to eighteen hours have little or no influence upon increasing the anticomplementary activities of heated human sera.

Heating in a water bath at 38° C. following incubation at from 8° to 10° C. for from four to eighteen hours increases the anticomplementary activities of antigens and sera.

Non-specific complement-fixation reactions with mixtures of normal non-syphilitic sera and organ extracts were not observed except in combined cold and warm primary incubations as from four to eighteen hours at 8° C. plus one hour in a water bath at 38° C.; alcoholic extracts saturated with cholesterol (0.4 per cent.) were found particularly likely to yield these reactions, whereas plain alcoholic extracts, extracts containing 0.2 per cent. cholesterol and extracts of acetone-insoluble lipoids were usually free of these non-specific effects.

Comparative Methods for Conducting the Primary Incubation for Complement Fixation. Kolmer, Mat-

(2) Amer. Jour. Syph., January, 1921.

sunami and Trist³ have made a comparative study of methods for conducting the primary incubation for complement fixation in syphilis and recommend a technique for a standardized test.

In comparative complement-fixation tests in syphilis, using the same technique but with one primary incubation in a water bath at 38° C. for one hour and a second in a refrigerator at 8° C. for from four to eighteen hours, the authors found no evidence of the existence of one antibody fixing complement best at 38° C. and a second reacting best at 8° C. The only differences encountered were positive reactions with some sera tested at 8° C. which reacted negatively at 38° C. and stronger reactions with some sera at 8° C. than at 38° C., especially with plain antigens. No syphilitic serum has been encountered yielding positive complement-fixation reactions with a primary incubation of one hour at 38° C. and negative reactions at 8° C. for from four to eighteen hours, provided the same antigen was employed in both.

Primary incubation at from 8° to 10° C. for from four to eighteen hours results in greater fixation or absorption of complement by sera and antigens alone than that occurring during one hour at 38° C., but also results in the specific fixation of more complement by mixtures of serum and antigen; complement fixation is slower but more complete at 8° C. than at 38° C. and especially with plain antigens.

Comparative studies in complement fixation in syphilis with two quantitative methods, three different antigens and seventeen different kinds of primary incubation, have shown that the best methods for conducting the primary incubation from the standpoint of sensitiveness of the reactions, are (a) three or four hours at from 8° to 10° C. plus one hour in a water bath at 38° C.; and (b) eighteen hours at from 8° to 10° C. in a refrigerator. With either of these methods, however, the kind and amount of antigen employed and adjustment of the hemolytic system, are factors of much importance in order to avoid non-specific reactions.

(3) Amer. Jour. Syph., January, 1921.

Influence of Temperature and Duration of Primary Incubation on the Velocity and Amount of Complement Fixation with Different Organ Antigens. In another series of experiments Kolmer, Rule and Yagle⁴ found that complement fixation with strongly syphilitic sera is frequently very rapid and may occur immediately at room temperature and especially with cholesterolized and acetone-insoluble lipoid extracts as antigens; incubation at 38° C., however, usually increases the amount of complement fixation.

Complement fixation in syphilis is usually, but not always, more complete in an open water bath at 38° C. than in an air incubator at the same temperature; one-half hour in a water bath, however, is not usually equal to one hour in an incubator, as is commonly stated.

The velocity and amount or degree of complement fixation at 38° C. varies greatly according to the organ extract used as antigen, being most rapid with cholesterolized extracts and least with plain or crude extracts.

In general terms, complement fixation in syphilis reaches the maximum degree of 38° C. in a water bath with extracts of acetone-insoluble lipoids in from 30 to 45 minutes; with cholesterolized extracts in one to two hours and with plain or crude alcoholic extracts at least two or three hours are required.

Primary incubation at 20° C. (room temperature) results in less complement fixation than in a water bath at 38° C. for one-half hour; two hours at 20° C. results in a fixation of complement about equal to one hour at 38° C.

Complement fixation in syphilis at from 0° to 8° C. is frequently very rapid, well-marked reactions being observed even after incubation of but fifteen minutes.

At temperatures of from 8° to 10° C. complement fixation in syphilis occurs more slowly than at 38° C., but the degree or amount of complement fixation is greater; this is especially true with plain or crude extracts.

Complement fixation in syphilis occurs somewhat more rapidly at 8° C. than at from 10° or 2° C.; the optimum

(4) Amer. Jour. Syph., January, 1921.

temperature for cold incubation is from 6° to 15° C. and the optimum time from four to eighteen hours.

At 38° C. for from one-half to two hours complement fixation in syphilis is much more rapid and greater in degree with cholesterolized and acetone-insoluble extracts as antigens than with plain or crude extracts; at from 8° to 10° C. for about eighteen hours the difference in degree of complement fixation among the different extracts is not so marked, although the reactions with cholesterolized extracts are usually slightly stronger than with plain extracts.

A Comparative Study of Complement Fixation in Syphilis with Anti-Human, Anti-Chicken, and Anti-Sheep Hemolytic Systems. A comparative study of complement fixation in syphilis with anti-human, anti-chicken and anti-sheep hemolytic systems was made by Kolmer⁵ and his coworkers, Matsunami and Rule.

With the technique made use of, comparative complement-fixation reactions with 503 sera from syphilitic persons under treatment have shown that tests conducted with anti-human and anti-chicken hemolytic systems were somewhat superior in sensitiveness to those conducted with anti-sheep and anti-ox systems.

It was found that from 2 to 10 per cent. more sera from syphilitic persons react positively in an anti-human system than in an anti-sheep system. An anti-ox hemolytic system was more sensitive than an anti-sheep system yielding from 2 to 5 per cent. more positive reactions with the sera of syphilitic persons. Anti-human and anti-chicken hemolytic systems are of about equal sensitiveness in complement-fixation tests with heated human sera. The differences in delicacy of reactions conducted with anti-sheep, anti-human, and anti-chicken hemolytic systems were more apparent in tests conducted with from 0.01 to 0.001 c.c. of each serum than in tests conducted with 0.1 c.c. serum.

Natural hemolysins in human and guinea-pig sera and particularly anti-sheep hemolysins, reduced the delicacy of complement-fixation tests conducted with an anti-sheep hemolytic system after the method described and particularly if the results were read after the tubes

(5) Amer. Jour. Syph., April, 1920.

had stood for sixteen hours or longer in a refrigerator; anti-human and anti-chicken hemolytic systems were more sensitive and served to detect smaller amounts of syphilis antibody in human sera.

A Study of Methods for the Preparation and Preservation of Hemolysins. A study by Kolmer and Rule⁶ of the method for the preparation and preservation of hemolysins demonstrated that in the production of anti-human and anti-sheep hemolysins in rabbits, the best results were secured by the intravenous injection of small doses of washed cells at frequent intervals. The intraperitoneal route is slower, yields less hemolysin, and is accompanied by a higher death rate with sheep cells.

In a comparative study of methods for the production of anti-human hemolysin in rabbits, best results were secured by the method of Thompson consisting of the daily intravenous injection of 0.1 c.c. of washed cells over a period of from three to four weeks. The death rate among rabbits so treated was lower than with other methods and the production of hemolysin relatively high.

For the production of anti-sheep hemolysin best results were secured by the daily intravenous injection of 0.1 c.c. washed cells and next best by the intravenous injection of 5 c.c. of a 10 per cent. suspension every three days for four injections.

Human erythrocytes are highly toxic for rabbits, resulting in producing a marked loss in weight during the period of immunization. Fatalities among the immunized rabbits appeared to be caused by agglutination *in vivo* and in high toxicity of human cells rather than by anaphylaxis.

Sheep and ox erythrocytes are but slightly toxic for rabbits, and may be used for the production of powerfully hemolytic sera low in agglutinins; there is slight or no loss in weight of the rabbits and the death rate is low.

Hemolysins for guinea-pig, chicken, and rat corpuscles are produced with about the same difficulty as human hemolysins; anti-chicken hemolysin was best prepared by

(6) Amer. Jour. Syph., July, 1920.

the daily intravenous injection of 0.1 c.c. washed cells suspended in 1 c.c. sterile saline solution.

Sensitized erythrocytes did not generally prove superior to plain cells; not infrequently hemolysin production occurred more promptly and progressed somewhat more rapidly after injection of sensitized erythrocytes, but the end-results were practically identical with those following immunization with plain cells.

The intravenous injection of plain sheep cells is followed in from three to four days by an increase of hemolysins in the serum and increases quite rapidly; with human cells immune hemolysin is not usually demonstrable for at least seven to ten days after single or repeated injections and increases very slowly.

For the collection of immune hemolytic sera rabbits should be bled about seven days after the last injection of cells.

Anti-human, anti-sheep, and anti-ox sera are well preserved by mixing the sera with an equal part of sterile high grade glycerol and keeping in a refrigerator; anti-human hemolysin is also well preserved dried in special filter paper after the method of Noguchi.

A Study of Methods for Adjusting the Hemolytic System with Special Reference to the Titration of Complement. Kolmer⁷ assisted by Matsunami and Rule made an experimental study of the methods for adjusting the hemolytic system in the Wassermann reaction.

They found that the hemolytic system for complement-fixation tests should be so adjusted that the amount of complement employed is neither unnecessarily large, which tends falsely to negative complement-fixation reactions in the presence of small amounts of syphilis antibody, nor too small, which does not allow for complement absorption by serum or extract alone and for complement destruction during the period of primary incubation.

The use of excessive amounts of hemolysin in the titration of complement may reduce the amount of the latter so greatly that the unit will not allow sufficient

(7) Amer. Jour. Syph., July, 1920.

for the non-specific factors operative in all complement-fixation tests.

Adjustment of the hemolytic system by daily titrations of complement has proved superior to adjustment by daily titrations of hemolysin for the conduct of complement-fixation tests for syphilis.

For practical purposes in routine complement-fixation tests when the complement is titrated plain (that is, in the absence of antigen and normal serum) it is necessary to use at least two units of complement and two units of hemolysin to allow for non-specific absorption by serum and extract alone and for deterioration of complement during incubation.

With an anti-sheep hemolytic system best results were observed by titrating complement in the presence of antigen and using two units with one unit of hemolysin. With an anti-human system this method renders the adjustment too close and requires the use of two units of complement and two units of hemolysin.

Titration of complement in the presence of extract and pooled non-syphilitic serum and the use of exactly one unit so obtained with one unit of hemolysin, was found a good method but open to error due to varying amount of anti-sheep hemolysin and anticomplementary substances in the pooled serum used in the titration, which so influenced the titrations as to yield a unit of complement too large for some sera and too small for others.

A modified serum for measuring the amount of complement absorbed by extract and serum alone yielded excellent results, but is not suitable for routine work because of the large amounts of complement serum required and labor involved.

In the titration of complement the unit of hemolytic activity is more quickly obtained by water-bath incubation than by air (thermostat) incubation; one hour in the former is equal to one and a half or two hours in the latter.

When complement is titrated in the presence of antigen or of antigen and normal serum, the mixtures should be incubated in a water bath for at least one hour before the addition of corpuscles and hemolysin

in order to elicit the full degree of non-specific fixation or absorption of complement by these substances.

The Influence of Heating Serum Upon Complement Fixation in Syphilis. Originally Wassermann and his associates advised the heating of sera for the main purpose of destroying the native complements and hence the phrase "inactivation of serum" has come into general use, but at the present time it is known that sera are heated for additional and probably more important reasons.

Kolmer, Rule and Trist⁸ consider the subject one of primary importance in relation to complement-fixation tests by reason of having a direct bearing upon the sensitiveness and specificity of the reactions; questions of economy of materials and time and of simplicity in technique are certainly of lesser importance.

Complement-fixation tests with unheated sera in which guinea-pig complement is used, are sometimes unsatisfactory because of the presence of anticomplementary substances (antilynsins) in certain sera; these may be largely avoided by using perfectly fresh sera, but in routine work this practice may not always be possible. The tests with unheated sera are also subject to the error of pseudo-positive or proteotropic reactions.

Complement-fixation tests with unheated sera in which the complement of each serum is utilized or both the complement and a natural hemolysin, are open to the objections of requiring fresh sera, the possibility of proteotropic reactions, the possibility of falsely negative reactions due to the lack of fixability of an individual complement, the absence of sufficient complement or hemolysin or both in 2 to 10 per cent. of sera and the impossibility of examining spinal fluids.

Complement-fixation tests with unheated sera possess, however, the advantage of greater sensitiveness because of the presence of thermolabile and thermostabile syphilis antibody; these tests are likewise usually simpler and more economical of materials and time.

Human complement is very susceptible to heat; at 50° C. the complement is reduced to one-tenth of its original strength in ten minutes and an exposure of fif-

(8) Amer. Jour. Syph., October, 1920.

teen minutes at this temperature is ample for the inactivation of sera.

The anticomplementary substances (antilynsins) of human sera are thermolabile and thermostabile; in routine work the antilynsins of human sera are usually of the former variety. For the removal of these antilynsins, heating sera at 55° C. for fifteen minutes is usually sufficient and particularly with sera tested within five days of the time of collection of blood; thermostabile antilynsins in old and contaminated sera are not removed by this amount of heating but these sera are to be regarded as unsatisfactory for the complement-fixation test.

For the removal of the substance from human sera responsible for the pseudo-positive or proteotropic reaction, heating at 55° C. for from five to ten minutes is sufficient.

Unheated spinal fluids are not usually anticomplementary unless contaminated with bacteria; furthermore they apparently do not yield proteotropic reactions. For these reasons they may be used unheated in complement-fixation tests. If antilynsins develop they are usually thermolabile and removable by heating to 55° C. for fifteen minutes; if the fluids are cloudy with bacteria the antilynsins are likely to be thermostabile, rendering the fluids unfit for complement-fixation tests.

Heating syphilitic serum reduces its power of absorption or fixation of complement with lipoidal extracts due to the destruction of a portion of the antibody, the removal of antilynsins and, possibly, to the destruction of the substances concerned in the proteotropic reaction.

The antibody in syphilitic serum concerned in the complement-fixation reaction is very susceptible to heat; deterioration occurs when sera are heated at 40° C. for thirty minutes and becomes progressive until at 62° C. and higher temperatures, complete destruction occurs. Very probably the antibody occurs in two kinds, namely, thermolabile and thermostabile, inasmuch as heating at 55° C. has little or no influence upon the fixing power of some sera.

When syphilitic sera are heated at 55° C. for fifteen minutes falsely negative complement-fixation reactions

may occur with 2 per cent. of sera containing small amounts of antibody or with sera tested in very small amounts, namely, from 0.01 to 0.0001 c.c.; when heated for thirty minutes a slightly greater destruction of antibody occurs producing about 5 per cent. falsely negative reactions and a higher percentage of weaker reactions, as compared with tests in which unheated serum is used. The greatest amount of destruction of antibody occurs during the first fifteen minutes of heating, but heating for thirty minutes according to the usual custom, results in a still greater and useless destruction of antibody.

When complement-fixation tests are conducted with an anti-sheep hemolytic system, the reactions with heated sera may be stronger than with unheated sera, due to the destruction or masking of a portion of the natural anti-sheep hemolysin in human serum by heat and a consequent closer adjustment of the hemolytic system.

Although heating syphilitic sera results in the destruction of a portion of the antibody concerned in the complement-fixation test, it is advisable to heat all sera for the purpose of inactivating native complement and thereby permitting a closer adjustment of the hemolytic system, destroying any antilysins (anticomplementary substances) that may be present and preventing the occurrence of pseudo-positive or proteotropic reactions with the sera of non-syphilitic persons.

For these purposes, heating sera at 55° C. for fifteen minutes is sufficient and preferable to the customary period of thirty minutes, inasmuch as less destruction of antibody occurs.

The inevitable reduction in the sensitiveness of complement-fixation tests conducted with heated sera should be compensated for in a standardized technique by certain technical procedures and particularly with reference to the kind and amount of antigen employed and the adjustment of the hemolytic system.

The Influence of Temperature and Duration of Primary Incubation Upon the Hemolytic Activity of Complement. In complement-fixation tests the method of conducting the primary incubation of mixtures of patient's serum, complement, and antigen for the fixation

of complement, has considerable influence upon the sensitiveness of the reaction; both the temperature and the time are factors of importance.

Kolmer and Rule¹ have found that the hemolytic activity of guinea-pig complement is reduced by primary incubation at 38° C. and especially in a water-bath for one hour; this partly explains the stronger Wassermann reactions observed after a primary incubation of one hour in a water-bath as compared with one hour in an incubator.

The hemolytic activity of complement is slightly reduced by primary incubation at 2° to 8° C. for four to eighteen hours, but markedly reduced under these conditions when titrated in the presence of antigen.

When complement-fixation tests in syphilis are conducted with a primary incubation of four to eighteen hours at 2° to 10° C. with or without an additional incubation of from one-half to one hour at 38° C., stronger reactions may be expected with some sera, due in part to the greater destruction of complement and consequent closer adjustment of the hemolytic system under these conditions than occurs during the usual primary incubation of one hour at 38° C.

Comparative Study of the Bordet-Wassermann Reaction in the Blood and Urine. Having observed a patient with secondary syphilitic nephritis with marked albuminuria and a negative Bordet-Wassermann reaction in the blood, Simon² carried out the reaction with the urine, which had previously been done by Blumenthal and in America by Wile. Parallel tests were made in 166 syphilitics and also in thirty-five non-syphilitics. Neither the acidity, alkalinity, hypertonicity, isotonicity, nor hypotonicity seems to play any rôle in the modification of the reaction. Only a variation in the quantity of urine seems to be of any importance in causing the variation in the results. Too much urine led to anti-complementary reaction. Of the 166 syphilitics, the reactions on the blood and urine were the same in eighty-nine cases, or 53.6 per cent. There were likewise sixty-two cases in which the result was negative in both urine

(1) Amer. Jour. Syph., October, 1920.

(2) Bull. soc. franc. de dermat. et de syph., 1920, p. 16.

and blood, and there were twenty-seven concordant positive results. There were discordant results in seventy-seven, or 46.4 per cent. In the cases of disagreement, the positive reaction was usually in favor of the blood. There were sixty-two cases having a positive reaction in the blood and a negative result in the urine, and fifteen cases in which the result was positive in the urine and negative in the blood. The appearance of the fixation of complement in the urine is slow. It is usually negative in the primary period and frequently negative in the secondary period, and most frequently positive in the tertiary period and in hereditary syphilis.

The Value of Postmortem Wassermann Reactions. In a previous volume,³ Stuart Graves found that the postmortem Wassermann reaction confirmed antemortem reactions in a large percentage of the cases. The same author⁴ reports the results of further work on post-mortem reactions.

In ninety controlled cases, there were flat discrepancies between antemortem and postmortem Wassermann reactions in only two. In 124 cases showing evidence of syphilis, postmortem or clinical, 137, or 90.5 per cent., gave a positive postmortem Wassermann reaction. The reliability of the Wassermann test depends to a considerable extent on the care used in obtaining and keeping the blood. Cholesterolized antigens are the most delicate and do not give false positive reactions if properly used and controlled. Observation of more than 15,000 reactions as correlated to clinical evidence substantiates the belief that the Wassermann test is the most delicate single test for syphilis. The postmortem Wassermann test is practically as reliable as the antemortem test if the serum be properly taken and shows nothing unusual in the serum control tube.

Agreement in Results of the Wassermann Reaction. Another study of the Wassermann test performed by two laboratories in 3,000 successive hospital admissions has been made by H. C. Solomon.⁵

An analysis of the results showed that there was a complete uniformity in the findings of the two labora-

(3) Practical Medicine Series, 1917, Vol. IX, p. 172.

(4) Jour. Amer. Med. Ass'n., Aug. 28, 1920.

(5) Ibid., March 20, 1920.

tories in 93.44 per cent. The 6.56 per cent. variation included cases reported as doubtful. Considering only the variation of cases reported positive by one laboratory and negative by the other, the percentage variation was 4. This was 1.4 per cent. positive in one laboratory and 2.6 per cent. positive by the other laboratory. Some of the cases reported positive by one laboratory and negative by the other were known to be syphilitic, so that the negative reaction was the incorrect one. Considering, then, the cases that either laboratory may have reported as positive in non-syphilitic cases, the percentage was 3.16. This is probably a higher percentage for false positives than actually occurred, as some of these cases were presumably syphilitic. This percentage variation is based on only one test. Repetitions resulted in a uniformity of findings in the majority of cases. This is considered a good testimonial for the accuracy of the tests as performed in these two laboratories.

Bordet-Wassermann Reaction in the Transudate of Syphilitics. It has been shown by Roger and Sabaréanu that the transudate in a syphilitic may give a positive reaction when the transudate is not of syphilitic origin. Riser⁶ has carried out the Bordet-Wassermann reaction on the transudates and exudates of syphilitic cardio-renal cases. In all sixteen of the cases studied, the Bordet-Wassermann reaction was strongly positive in the blood. The reaction was also positive in the edematous liquid and pleural transudate and in the ascitic fluid of five of the patients. In four of these five patients, the autopsy demonstrated that there was no pleural pulmonary or thoracic lesion of syphilitic origin capable of explaining the positive character of the Bordet-Wassermann in the pleural fluid. In some of the cases, the first fluid aspirated gave a strongly positive reaction but the fluid aspirated on subsequent occasions gave either very slightly positive or negative reactions. In one case after the reaction had become negative, it suddenly became positive again. The work of Riser, therefore, seems to support the view that because the Bordet-Wassermann reaction is positive on the transudate or the exudate, is

(6) *Ann. de dermat. et de syph.*, October, 1920.

no reason for the supposition that the lesions producing this exudate are of syphilitic origin.

Production of Positive Reactions in Non-Syphilitic Patients After Intravenous Therapy. The specificity of the Bordet-Wassermann reaction is again called into question by the work of Strickler, Munson and Sidlick,⁷ who treated non-syphilitic patients with weekly doses of arsphenamine and found that approximately sixteen, or 66 per cent., of these patients gave at least one positive reaction, and fourteen, or 58 per cent., gave two or more positive reactions. The greatest number of positive reactions in one case was nine, and in another case they obtained six positive reactions. The Wassermanns were done in part by two laboratories, working independently, and all of them were done by men who knew nothing of the problems on which the workers were engaged.

As all their patients gave negative syphilitic histories, and since physical examination failed to disclose any scars or stigmata of syphilis; since these patients suffered from skin affections in the etiology of which syphilis plays no rôle; since the treatment did not favorably influence these lesions; in fact, the distinct tendency being toward an aggravation of their dermatologic affection; since their first Bordet-Wassermann reactions were absolutely negative, and, what is most conclusive, the fact that the vast majority of the Bordet-Wassermann reactions turned from a clear-cut negative to positive at an interval far beyond the time set for the appearance of the provocative Bordet-Wassermann; and, what is also to be considered, that their patients were receiving weekly injections of arsphenamine—all these facts seem to prove conclusively that the Bordet-Wassermann reaction obtained can not and should not be classified in the category of provocative reactions.

In theorizing on the possible cause of the positive Bordet-Wassermann reactions produced in their experiments, they were inclined to incriminate the arsphenamine as the causative agent. It was their impression in this research that of those patients who consistently were made ill after the treatments, their serums were most

(7) Jour. Amer. Med. Ass'n., Nov. 27, 1920.

likely to show positive results. Of course, this observation was by no means the universal rule. In this connection, the observations of Strathy and his associates on delayed arsenic poisoning following the use of arsphenamine is worthy of consideration. They report fifty-eight cases of delayed arsenic poisoning, eight of which were fatal. The symptoms in each case were similar. In all of the fatal cases and in thirty-nine of the non-fatal ones jaundice was a prominent symptom. The urinary findings were: albuminuria in twenty-eight cases; bile salts in thirty-five; increased urobilin and urobilinogen in sixteen.

In view of these findings, it is suggested that the arsenic in the arsphenamine in some way acts on the liver alone or on the spleen and bone marrow also; that one or all of these organs may as the result of the arsphenamine administered elaborate a lipoidal substance which, when it occurs in sufficient quantity in the blood stream, is capable of yielding a positive complement fixation test for syphilis. What the nature of this substance is and whether or not it is analogous to the lipoidal substance elaborated by *Spirochaeta pallida* they are in no position to answer.

Because of their findings, it is their belief that at times too much arsphenamine is administered in the treatment of syphilis, and that this remedy may at times be responsible for the persistence of a positive Bordet-Wassermann reaction.

The hope that has been aroused of a "*therapia sterilisans magna*," a rapid and radical cure of syphilis, has not been realized. The effect of arsphenamine on the initial lesions of syphilis, the mucous patches and the early and late eruptions of this malady are definite. Certainly arsphenamine silences syphilis, so that the danger of contagion is immeasurably diminished, and it is needless to dwell on the social importance of this result.

Notwithstanding the influence of arsphenamine, the logical treatment of syphilis consists in the judicious combination of arsphenamine and mercury. From the wild enthusiasm following the introduction of arsphenamine, the pendulum of experience is now reaching level; namely, the reduction of the total amount of arsphenamine.

mine administered and the thorough and early use of hydrargyrum, so that today the leading syphilographers are advocating three or four intravenous injections of arsphenamine given at short intervals (one or two days apart) instead of from eight to ten injections of this remedy at weekly intervals.

The general opinion is that today we are curing more syphilitic patients than we did when mercury alone was employed. No one can deny the great value of arsphenamine; but sight must not be lost of the fact that now we do not wait for the development of the secondary eruptions before beginning treatment. With the improved methods of diagnosis, we often begin the treatment for syphilis either during the stage of the initial lesion or during that of the secondary incubation.

The tendency of the leading syphilographers is to give arsphenamine at short intervals and fewer doses, and to push mercury with the same enthusiasm as they do arsphenamine. With this view, these workers concurred as a result of their studies. It is their impression that with this mode of attacking syphilis we will probably have fewer so-called Wassermann-fast, in reality arsphenamine (arsenic)-fast patients.

The tendency among leading authorities on syphilis is toward intensive treatment; the general trend among leading serologists is to make the Wassermann reaction as sensitive as possible, by new innovations in technique and the use of more delicate antigens. These innovations in the treatment of syphilis and these refinements in the delicacy of the Wassermann reaction are tending toward a different conception of the Wassermann reaction as an index of the curability of syphilis.

What is agitating the leading syphilographers today is the question as to whether a syphilitic patient, clinically well, must continue to submit to treatment until he is serologically negative. At this juncture the studies of Udo Wile on the curability of syphilis, based on the Wassermann reaction as an index, are worthy of discussion. In his series of patients Wile proved conclusively that, given patients in the same syphilitic state, treated under similar conditions and with the same plan of procedure, the percentage of cures obtained varied

with the technique of the Wassermann reaction which was employed.

The present authors are convinced, with Udo Wile, that "in the presence of intensive therapy, a positive test does not necessarily mean living spirochetes and potential syphilis, any more than a positive tuberculin test in an individual who has had tuberculosis would indicate the presence of living tubercle bacilli."

In the light of their ignorance of the nature of this reaction, and particularly in the light which this study throws on the interpretation of at least some of their persistent Wassermann-positive reactions, they submit that serologic and clinical cures are not necessarily parallel. Energetic treatment that is directed toward the end of attempting to make a persistent positive reaction negative may be not only useless but also misdirected.

In this investigation no subject received more than seven injections of arsphenamine in weekly succession. Those receiving more than seven injections were permitted to let two weeks intervene between treatments.

[If a positive reaction results from the arsphenamine injected, as apparently has been demonstrated by the authors, it would be illogical to expect to obtain a negative reaction by treatment of a patient having a positive reaction when the treatment is begun. Nevertheless, this negative reaction is constantly being brought about, and, moreover, the "Wassermann-fast" case is the exception and not the rule.

Confirmation of this work by others is necessary before it can be accepted.—M.]

Serologic Activation in Primary Syphilis. Reactivation in late syphilis is a well known phenomenon and is of considerable value in a certain percentage of the cases. It occurred to Gouin and Leblanc⁸ to attempt the same thing in primary syphilis. Inasmuch as the Wassermann test is frequently negative early in the development of the chancre, the authors carried out a series of experiments on fifteen cases divided into three classes. In the first class the reaction was negative. In the second class it becomes positive during the course of

(8) Bull. soc. franc. de dermat. et de syph., 1920, p. 174.

the treatment. In the third class the reaction is already slightly positive but becomes more so. The authors bring up the question as to whether the patient who develops a positive Bordet-Wassermann in the course of this activation is to be considered as sterilized, or whether only that patient whose reaction remains negative is to be considered as sterilized. Lévy-Bing and Gerbay have shown that the Wassermann becomes positive between the fortieth and forty-fifth day after the infecting coitus. It was interesting to observe in this series of fifteen chancres that the Wassermann became positive at practically the same time regardless as to whether treatment had been instituted or not. Only one chancre out of the fifteen remained negative to the Bordet-Wassermann reaction.

Prolonged Ice-Box Incubation. In the determination of syphilis by means of the Wassermann reaction prolonged (twelve hours) primary ice-box incubation had been proved by Burdick⁹ to possess decided advantages over the short period (one-half hour) incubator or water-bath treatment. Serums giving doubtful reactions by the later method of primary incubation frequently are frankly positive by the former method. In the series studied, both methods gave uniformly negative results in 100 per cent. of the clinically non-syphilitic cases, and positive results in 100 per cent. of the second stage untreated cases.

In the second stage treated cases, however, there was a decided difference, especially in the higher percentage of positives obtained by the prolonged primary ice-box incubation method. Likewise this method gave a decidedly higher percentage of positives in the third stage untreated (attaining 100 per cent. as compared to 55 per cent. by the half-hour water bath method) and the third stage treated cases. In the examination of spinal fluids from patients with cerebrospinal syphilis there frequently is obtained a positive reaction by the prolonged ice-box incubation, whereas the conventional water bath method may be negative.

The Provocative Test in the Diagnosis of Syphilis. In 1917 Stokes and O'Leary published the results of

(9) Archiv. Dermat. and Syph., August, 1920.

their provocative tests as carried out in 103 cases. O'Leary¹⁰ gives the results of a study of the test in another series of 285 cases. The provocative procedure consists of a single intravenous injection of three decigrams of arsphenamine followed by a series of seven Wassermann tests made at twenty-four hour intervals. The first blood is drawn just before the arsphenamine injection, and if indicated, daily observation of the patient is carried out. The author finds that there are four factors which contribute to the diagnostic worth of the procedure: First, a true provocative effect on the Wassermann reaction; second, the advantage of a series of Wassermann tests which strikes the average and assists in the interpretation of the spontaneous or technical variations of the ordinary test; third, an opportunity to observe a focal flare-up in a visible lesion, the so-called Herxheimer reaction; fourth, the beginning of the therapeutic test.

O'Leary advises against the use of the hypersensitive antigen and insists that a negative provocative test does not establish the fact of cure, but a positive provocative result is of assistance in recognizing an infection which might otherwise have remained concealed. The provocative procedure is of no value alone and should be regarded merely as a part of the general syphilologic examination.

The Effect of Mercury Salicylate on the Wassermann Reaction. An attempt was made by Goodman¹ to determine the value of intramuscular injections of mercury salicylate on the Wassermann reaction.

Eighty-seven previously untreated latent syphilitic patients with four plus Wassermann reaction were given one grain of mercury salicylate intramuscularly at weekly intervals for courses of from six to eight injections. The Wassermann reaction immediately after the treatment remained strongly positive in 66 per cent. of the cases. In only 9 per cent. was there reversal to negative; and, in some such patients who were given a third Wassermann test after an interval without treatment, the reaction was positive. The author concluded

(10) *Archiv. Dermat. and Syph.*, September, 1920.

(1) *Ibid.*, August, 1920.

with Nelson and Anderson, who carried on a similar study in 1915, that mercury salicylate alone in the dosage and for the period given does not qualify as a curative agent in syphilis.

[In these days of intensive treatment of syphilis, the surprising point in Goodman's results is, not that he did not get more negative Wassermann reactions, but that he got 9 per cent. negative reactions. A series of six weekly 1 grain intramuscular injections of mercury salicylate might be looked upon as a prologue, a preliminary bout, a curtain raiser, or an overture to the therapeutic marathon in the treatment of syphilis. There are some cases of syphilis in which the Wassermann reaction can not be rendered negative even by the most intense arsphenamine injections much less by six or eight mercurial injections. That this small number of injections should give 9 per cent. of reversals to negative speaks in favor of rather than against mercury salicylate as a curative agent.—M.]

A Clinical Study of Wassermann-Fast Syphilis, with Special Reference to Prognosis and Treatment. What the management of the so-called Wassermann-fast syphilitic is to be is the question that has not as yet been settled. Stokes and Busman² have made a study of the problem as it presented itself in 458 cases.

Of 458 patients who had received from twelve to twenty-nine arsphenamine injections combined with mercurial inunctions, the average being fourteen injections and ninety inunctions in eleven months, 6.6 per cent. of primary and secondary cases and 22 per cent. of latent late and hereditary cases remained persistently Wassermann positive.

Cardiovascular changes are apparently those most likely to underlie a persistent positive Wassermann test in late syphilis. There were only ten patients presenting no other evidence of syphilis than their positive Wassermans. Patients with syphilis should therefore be studied from other angles than that of the presenting type of involvement, in the effort properly to appraise their condition and susceptibility to treatment. Sixty-five per cent. of the patients with cardiovascular syphilis

(2) Amer. Jour. Med. Sci., November, 1920.

had aortitis and 60 per cent. myocardial changes. Of the neurosyphilitics, 40 per cent. had paresis and 50 per cent. clinical tabes dorsalis. Fifty per cent. of patients with neurosyphilis had cardiovascular syphilis also. Gastric and hepatic syphilis were recognized in 52 and 47 per cent., of the visceral cases as against only 14 per cent. presenting recognizable splenic involvement. Patients with cutaneous syphilis showed the familiar immunity from neurosyphilis and the reverse.

While pyogenic foci were present in 74 per cent. of the patients with resistant Wassermann reactions no frank etiologic connection was apparent. The same was true of alcohol, which was used by only 12 per cent. of these patients.

There was no evidence that Wassermann-fastness is the result of infection with any special strain of organism. In fact, the "polystructural" involvement in such cases suggests the contrary.

The amount of treatment to which a Wassermann-resistant patient should be subjected can not be exactly defined. In particular, reversal of the Wassermann, while desirable, should not be the primary aim of the therapy. Symptomatic response, with arrest of the process, and the giving of as much treatment as to an early case, provided tolerance permits, are the important considerations.

TREATMENT OF SYPHILIS.

ARSPHENAMINE AND NEO-ARSPHENAMINE.

The Clinical Approach to Syphilis. It is the belief of Stokes³ that the revival of clinical syphilology calls for a new type of syphilographer, synthetic rather than analytic in temperament, whose qualities as an inspirer of men, a coöperator, interpreter and coördinator, will out-rank his merely technical expertness in the minutiae of syphilologic diagnosis. Such a syphilographer will direct in his field the efforts of a highly complex diagnostic organization rather than perform a few special tests.

(3) *Archiv. Dermat. and Syph.*, October, 1920.

He will become expert in the appraisal of the relative significance of a variety of structural and functional investigations which he does not himself necessarily perform. He will endeavor to give concreteness to the intuitive, and he will find in highly developed and systematized records that mastery of data which his synthetic powers require for the attainment of a new type of exactitude and conclusiveness in clinical research.

Reactions Following Arsphenamine Injections in Non-Syphilitics. An attempt has been made by Strickler, Munson and Sidlick⁴ to determine, if possible, the rôle played by the syphilitic infection in the production of the reaction to the intravenous injection of arsphenamine. Many of the reactions following arsphenamine injections have been ascribed to the spirocheticidal action of the arsphenamine.

A large series of syphilitic and non-syphilitic individuals were injected intravenously with arsphenamine in the usual way. The reactions were carefully tabulated and it was found that in the two series the percentages were practically the same. Therefore, the endotoxins, produced presumably by the rapid killing of spirochetes in the blood stream of syphilitic patients, play either no rôle or a very unimportant one in the causation of reactive symptoms.

In the opinion of the authors, the two most important factors in the production of arsphenamine reactions are (1) the patient and (2) the medicament. Of these two factors, the medicament is far more potent in causing reactive symptoms; the untoward phenomena may be produced either by some impurity in the arsphenamine or by some chemical reaction between the arsphenamine and the chemical constituents of the blood, or both factors may be operative at the same time.

Effects of Arsphenamine on Renal Function in Syphilitic Patients. The kidney function of a series of syphilitic patients treated with arsphenamine injections was tested both before and after treatment with the phenolsulphonephthalein and ureate test by Elliott and Todd.⁵ In a series of twenty patients on whom phenol-

(4) *Archiv. Dermat. and Syph.*, December, 1920.

(5) *Ibid.*

sulphonaphthalein determinations were made, 25 per cent. showed a reduction of from 10 to 17 per cent. of the function, while the remaining 75 per cent. remained the same at both determinations or showed only a slight reduction after treatment. The urea content of the blood in twenty cases showed a slight, if any, change. The results of these experiments seem to indicate that arsphenamine, at least the particular arsphenamine used by these men, exercises very little influence on the kidney function.

A Valuable Method of Employing Arsphenamine in Syphilis. The method of treatment of syphilis described by O. S. Ormsby⁶ proved efficient in a number of cases resistant to other methods. The absence of untoward results and reactions of any moment in the large number treated makes it appear as safe as other methods.

In the early stage, before generalization has occurred, three injections of arsphenamine are given with an interval of one day between the injections. The average dose is 0.4 gm., but in some instances 0.5 or 0.6 gm. are given when the patient is large and vigorous. In patients not previously treated the first dose is never more than 0.2 gm. Following this, treatment for one month with mercury, either by injection or inunction, is given. Six weeks from the last arsphenamine injection, three more arsphenamine injections are given. It appears important to give the second series in six weeks, as at that time the Wassermann reaction is likely to be negative and is more likely to remain so if treatment is then resumed. If two or more months elapse before the second series, a Wassermann relapse is probable. In well-developed cases not previously treated, the same procedure is followed, except that after the second series of arsphenamine twelve injections of mercury salicylate are given at weekly intervals, or their equivalent in inunctions over a period of three months, after which a third series of arsphenamine is given as before; this series is again followed by another period of three months of mercury. In the second year, two series of treatments are given in the Wassermann-negative cases as a prophy-

(6) Jour. Amer. Med. Ass'n., July 3, 1920.

lactic measure. In the Wassermann-positive cases the procedure is as outlined for the first year.

In a series of 160 private cases these results were noted after from two to five courses had been given: Sixty patients, or 37.5 per cent., remained clinically well and Wassermann-negative as tested for periods varying

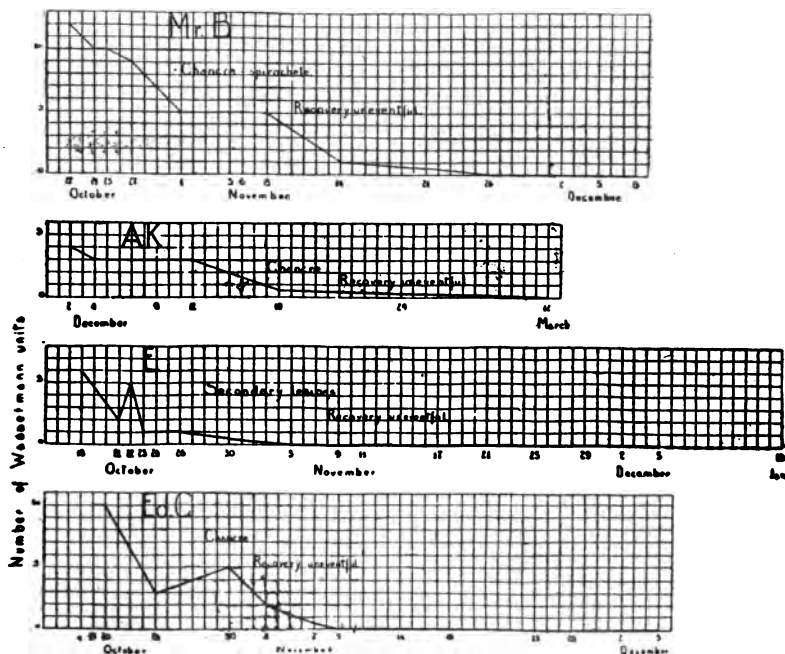


Fig. 13. Wassermann curve in four patients treated by the method described in this paper; no clinical relapses. Routine treatment: first day, 0.2 gm. arsphenamine; third day, 0.4 gm. arsphenamine; fifth day, 0.4 gm. arsphenamine; twenty mercury injections; arsphenamine injections repeated.

from one to three years; thirty-six, or 22.5 per cent., were identical with the foregoing except that they were watched only for a period of from six to nine months after finishing the treatment. There has been no opportunity for testing these cases further. Fifty-two, or 32.5 per cent., are classed as doubtful, as they disappeared after receiving two or more periods of treatment and no

subsequent tests have been made. Some of these have been reported by colleagues in other cities as remaining negative. It is likely that a small proportion are serologically free. Twelve, or 7.5 per cent., failed to respond serologically even after several periods of treatment. The 160 cases were chiefly late and latent, and all the patients had had quite a large amount of treatment pre-

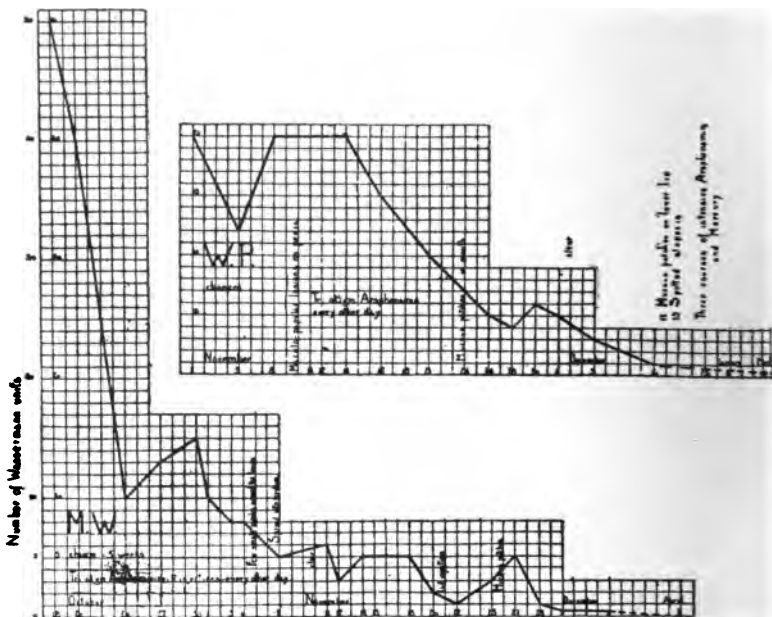


Fig. 14. Wassermann curves of two patients treated with small doses of arsphenamine at short intervals, with date and character of clinical relapses.

viously; only a small proportion were active or so-called secondary cases. In another small group treated in the early chancre stage, before the Wassermann test became positive, 100 per cent. were apparently cured serologically and clinically. Some of these have presented negative findings for over two years.

In a group of 258 cases treated at Rush Medical College by Dr. Shafer, in which the method outlined above

was adhered to, 110, or 42 per cent., responded to three courses or less, while 148 failed to respond and required more treatment. Of the 258 cases, twenty-one were primary; and of these, twenty, or 95 per cent., responded to three courses or less. Of the total number, 104 were early secondary of which fifty, or 40.3 per cent., responded; 134 were late and latent, of which forty, or 29.9 per cent., responded. Of the 110 recorded as responding to the treatment, forty-two were negative from six to twelve months after treatment, and sixty-two for

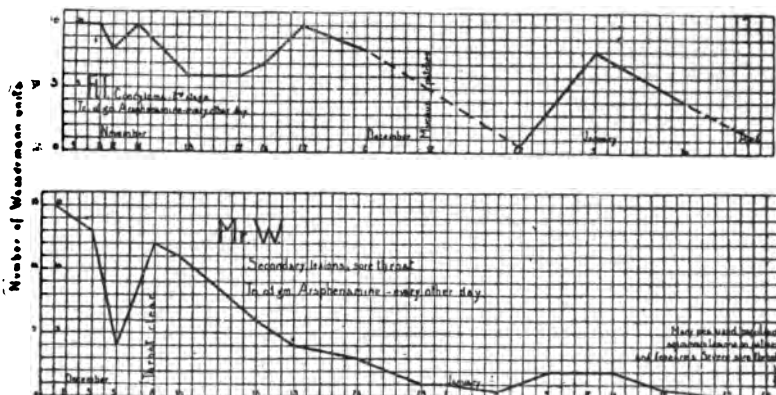


Fig. 15. Wassermann curves of two patients treated with small doses of arsenphenamine at short intervals, with date and character of clinical relapses.

less than six months. A sufficient time, therefore, had not elapsed to make definite statements as to the ultimate results. Judging from the history of the forty-two cases remaining negative, it seems likely that in a year a majority of the sixty-two will show similar results.

In order to determine, if possible, the effect of different sized doses and varying intervals, several groups of cases have been studied at the clinic at Rush Medical College. Quantitative Wassermann tests have been made in these cases by Dr. Retinger, and the treatment has been administered by Dr. Shafer. As this study is now in progress, only a few observations are permissible here.

The technique of the Wassermann work was conducted in such a way in the series of experiments as to determine the smallest quantity of the patient's serum which was able completely and exactly to deviate one unit of complement in the presence of the optimum quantity of a standard antigen (Figs. 13 to 16).

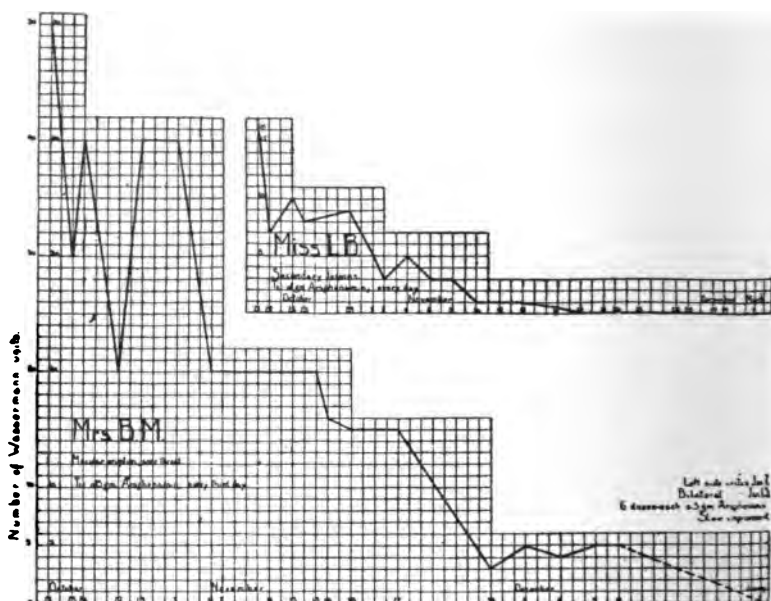


Fig. 16. Wassermann curves of two patients treated with small doses of arsphenamine at short intervals, with date and character of clinical relapse in one.

Arsphenamine in the Preventive Treatment of Syphilis. The excellent results obtained by the use of the external application of calomel ointment and the urethral injection of argyrol in the prevention of venereal disease in the American army has demonstrated beyond all doubt the efficiency of such methods in the prevention of venereal disease. There are cases, however, in which either because of the inaccessibility of the external application within the time

limit or because the contagion has seemed to have been particularly virulent, that it is not safe to rely upon the external application. In just such cases as these Stühmer, in 1918, suggested the use of intravenous injection of arsphenamine to prevent infection by *Spirochaeta pallida*. Since that time various articles have appeared, the most important of which is that of Fournier and Guenot.⁷ These authors injected forty women with six small doses of arsphenamine. All the women had been exposed on repeated occasions to men with active syphilitic lesions; all were carefully examined and were demonstrated to be free from syphilis. All of the women were observed over a period of from two to three years. At the same time there were five women who refused treatment and all of the five women developed active syphilis within the normal incubation period.

Golay⁸ sums up the results of his observations in the use of such methods as follows: The use of the intravenous injections of arsphenamine as a prophylaxis in syphilis is indicated in all cases in which it is known positively that an individual has been exposed to syphilitic contagion. A prophylactic injection is also justified in all cases of chancroid; also when it is known that a man has been exposed and is about to be married; and also if he has had extraconjugal exposure. It should not be used, however, in cases of syphilophobia nor as a source of income. The dose should be not less than 0.3 gm. of neo-arsphenamine and the size of the subsequent doses, probably six in all, would depend upon the tolerance of the patient. The author has not yet been able to determine at what period of the incubation it ceases to become possible to sterilize the patient.

Michel and Goodman⁹ state that they have used intravenous injections of arsphenamine in "probably thirty patients as a prophylaxis." No figures are given but they are convinced that the method is of great value and should be more widely used.

A Ready-For-Use Solution of Arsphenamine. A stock solution of arsphenamine which is known as Arsphenamine-Lowy is prepared and marketed and has been ex-

(7) Presse méd., October, 1919.

(8) Ann. des mal. vén., November, 1920.

(9) Jour. Amer. Med. Ass'n., Dec. 25, 1920.

amined by Dudley D. Stetson,¹ Acting Assistant Surgeon, U. S. P. H. S.; New York Skin and Cancer Hospital. In preparing this solution the water is freshly distilled, boiled and evacuated by means of a vacuum pump. The powder is then dissolved in either hot or cold water, depending on the brand used. This solution is placed under a vacuum to remove any gases which may have been present in the powder or generated during its solution. The acidity is then determined by titration and sufficient sodium hydroxide added to form the disodium salt. The solution is then again placed under a vacuum for four hours, filtered into ampoules and sealed under negative pressure. The object of this is to obtain a solution free from air and other gases.

In 850 injections of the solution of arsphenamine-Lowy, there were fifteen known reactions, or a percentage of 1.7. No cutaneous eruptions followed the injections. No unusual results followed the intraspinal use of the solution.

The Hygienic Laboratory has recommended a limit of thirty days' dating on the ampoules after animal experimentation, but states that "in a general way, it may be said that if the solution is kept cool there is no appreciable increase in toxicity in the course of six weeks or two months."

[In the discussion which followed the presentation of this paper, Sutton and Cole agreed that anyone who did not know enough to mix a solution of arsphenamine certainly did not have sufficient knowledge and technique to give it. Inasmuch as neo-arsphenamine is available in all communities and can be given in a very small quantity of water, even boiled tap water, it would seem advisable to use neo-arsphenamine rather than a stock solution of arsphenamine.—M.]

The Arsphenamines in Therapeutics. Based on the material collected from a series of 30,000 intravenous injections of arsphenamine under hospital conditions at the Mayo clinic, Stokes² discusses the applications and limitations of the arsphenamines in therapeutics. The

(1) *Archiv. Dermat. and Syph.*, September, 1920.

(2) *Ibid.*

nature and length of the article make it unsuitable for use in these volumes.

Intraspinal Treatment in Neurosyphilis. The results of the treatment of fifty-two cases of neurosyphilis extending over a period of five years are given by J. H. Mitchell.³ The fifty-two patients received 310 intraspinal injections which, as a rule, were given at monthly intervals. Of the twenty patients with paresis, eleven are now dead. It is an interesting fact that these eleven patients received an average of three and a half injections each, whereas seven paretics who are much improved clinically and are still living received an average of fifteen injections each. Therefore, had it been possible to give some of these patients more injections, a few of them might have had better results. Two paretics, who are still alive, show thus far little improvement either clinically or serologically. Of the twenty-five patients with tabes, thirteen show marked clinical improvement, and at the last examination the spinal fluid was negative. Ten patients are much improved clinically, but the fluid is still positive. Two of the patients with tabes have passed from control, and their present condition is unknown. Of the seven patients with central nervous system syphilis other than tabes or paresis, four patients are much improved clinically and have negative spinal fluids. In one case the fluid cleared and later became positive. In another case the fluid remained strongly positive.

The author concludes that the Swift-Ellis intraspinal method of treatment of syphilis of the central nervous system is superior to intensive intravenous treatment alone.

Whether the efficacy of the method of treatment depends on (a) the irritative action of the serum, thereby increasing the permeability of the chorioid plexus for arsphenamine; on (b) the spirocheticidal action of the arsphenamized serum, or on (c) spinal drainage, remains to be determined.

The method is perfectly safe, Mitchell declares, when care is exercised in technique and in the proper selection

(3) *Archiv. Dermat. and Syph.*, July, 1920.

of cases, and should be resorted to in all cases in which the patient fails to respond to intravenous medication.

Asthmatic Crises Cured by Neo-Arsphenamine. The danger of giving arsphenamine to an asthmatic has long been recognized, but the cure of asthmatic crises by the use of the drug is a rarity. Milian and Blum⁴ report the case of a patient, 74 years old, who had had an intense pruritus for the past four years; there was a symmetrical prurigo which was most marked on the arms. The patient was dyspneic and catarrhal. He complained of asthmatic crises of three years' duration; upon the slightest effort there was marked dyspnea. There was severe cough with abundant expectoration, which was negative for tubercle bacilli. The Wassermann reaction on three occasions was completely negative. The patient was given three injections of neo-arsphenamine, with remarkable improvement of the asthmatic condition.

In the discussion which followed the presentation of this case, attention was called to the fact that Milian had administered adrenalin along with the neo-arsphenamine, as is his custom, and that probably the beneficial results of the treatment were due in part to the change in residence and nourishment and to the adrenalin.

[The administration of arsphenamine to asthmatics may be attended by most alarming crises. One of our patients was given on three different occasions injections of three different preparations. The last time the patient was given an injection of 0.05 arsphenamine which was followed by adrenalin, and for more than an hour she was in the most serious respiratory embarrassment.—M.]

SILVER SALVARSAN AND SULFARSENOL.

Intramuscular Injections of Sulfarsenol. [The first method of the injection of arsphenamine adopted by Ehrlich was the subcutaneous injections. The pain occasioned by the subcutaneous injection, however, made it almost impossible to use this method; later it was abandoned and intramuscular injections were adopted. Here again the pain was severe in some cases and sloughing occurred and was followed by severe scarring, making it

(4) Bull. soc. franc. de dermat. et de syph., 1920, p. 2.

very difficult for the patient to conceal the fact that an intramuscular injection had been received. Later intravenous injections became popular and have at the present time supplanted the intramuscular method. Very rapid elimination of arsphenamine when given intravenously has led some men to return to the use of the intramuscular route because of the slower absorption. One great disadvantage of the intramuscular route, however, is very difficult to overcome; namely the severe pain which follows the injection.—M.]

Sulfarsenol recently has come into some prominence and Lévy-Bing and Gerbay⁵ have undertaken to find a painless preparation of this drug which might be given intramuscularly.

The drug is dissolved directly in sterile, distilled water and is given in a dosage ranging from 1200 up to 3000 grams of sulfarsenol every other day or every fourth or fifth day.

The authors found that the therapeutic results of the intramuscular injections of sulfarsenol were comparable but not equal to the intravenous injections of the other arsphenamines. It has the advantages of being very easy to inject and of obviating the severe reactions which not infrequently follow the intravenous injections of the various arsphenamine preparations.

Urinary Elimination of Arsenic After Intramuscular Injections of Sulfarsenol. At the present time sulfarsenol is the only arsphenamine preparation that can be injected intramuscularly and subcutaneously in concentrated aqueous solutions; therefore, the work of Galonnier⁶ is of interest in showing that the elimination of arsenic by the urine is only five-sixths of the amount injected. What becomes of the remainder of the arsenic injection the author is not yet in a position to state.

Comparative studies of the elimination of arsenic by the urine following intravenous and intramuscular injections of sulfarsenol were made and it was found that the maximum amount eliminated after intravenous injection occurred about the end of the first hour; whereas after intramuscular injection, the maximum amount is

(5) Ann. des mal. vén., January, 1920.

(6) Ann. de dermat. et de syph., August, 1920.

not reached until the end of the first day and in some cases the middle of the second day. In spite of the difference in the rate of elimination, the elimination continued until the sixth day in both types of administration.

It was a remarkable fact that the amount of arsenic eliminated was not at all in proportion to the amount injected; for instance, 0.4 grams of sulfarsenol or neosalvarsan gives as much arsenic in the urine as 0.75 grams of either drug.

Concerning the fate of the arsenic which is not eliminated, Jeanselme says: "Arsenic becomes fixed at hazards, sometimes in one viscera, sometimes in another and one at the present time is totally ignorant of what determines the location of the residual arsenic." In any case, the kidneys eliminate only a relatively small part of the arsenic injected.

Treatment of Syphilis with Silver Salvarsan and Sulfoxylat. A clinical study of the therapeutic efficiency and of the toxicity of silver salvarsan and sulfoxylat has been made by Bruck and Sommer.⁷

The dosage for silver salvarsan should be at first 0.1 of a gram and should not exceed at any time 0.25 of a gram. It should be dissolved in 20 c.c. of water and injected very slowly, drop by drop; otherwise, very unfortunate symptoms, particularly angioneurotic symptoms and loss of consciousness, may occur. Moreover, the silver salvarsan solution is very irritating to the veins and unless it is injected slowly complete thrombosis may occur. The author makes a practice of having the patient count up to two hundred and if at any time the patient fails to count accurately the operator knows that he is losing consciousness and the injection is stopped.

The rise in temperature after silver salvarsan is very much more marked than with the other preparations. The arsenic exanthem occurred four times in sixty-four cases, two of which were serious. The clinical results after silver salvarsan seem to be somewhat more rapid than with the other arsenic preparations. As a rule, the spirochetes disappeared within twenty-four hours after

(7) *Dermat. Zeitschr.*, March, 1920.

the first injection. The results of the combined silver salvarsan and mercury treatment lead the author to conclude that the silver salvarsan should not, under any circumstances, be followed by mercurial treatment. He believes that silver salvarsan is of great value in the early treatment of syphilis, but that it is much too dangerous to be used by the general practitioner or to any great extent by syphilographers.

Sulfoxylat (No. 1495) can be administered very simply inasmuch as it is in ampoules in solution of 0.1 gm. to 1 c.c. of water. Great care should be exercised not to get any of the drug outside the vein because it is extremely painful. The reactions from sulfoxylat were very few and of no consequence. The average dose is 0.2 gram and the maximum dose 0.3 gram. The therapeutic efficiency of sulfoxylat is about that of neosalvarsan. Following the use of sulfoxylat there were three cases of cutaneous lesions, one of herpes zoster and two of severe arsenic examthem. These three occurred in a series of twenty-five cases. The greatest advantage in the use of sulfoxylat is that it can be given intramuscularly in aqueous solution without causing much pain, and in no case in the series of cases treated by the author did necrosis occur.

The Results of Silver Salvarsan Therapy. In a series of fifty-three cases of primary and secondary syphilis Arzt⁸ found silver salvarsan to be very active therapeutically. The period during which the cases were observed after treatment with silver salvarsan was too short to be of any value as indicating the freedom of recurrences, but, however, no recurrence was observed in any of the fifty-three cases. Serologically, all the cases but one became negative after the combined use of silver salvarsan and mercury. The angioneurotic symptom-complex did not appear in any of the cases treated. The temperature in some of the cases rose to 39° C., but caused no difficulty. One very severe complication appeared in a young man treated with combined silver salvarsan and mercury. After the fifth injection of silver salvarsan the patient developed a high temperature, icterus and arsenic examthem and eventually died.

(8) Dermat Zeitschr., October, 1920.

Idiosyncrasy to Both Mercury and Silver Salvarsan.

A case presenting considerable therapeutic difficulty is reported by Mergelsberg.⁹ The patient had typical active syphilis and was treated with mercury given in the form of inunctions. A very severe dermatosis resulted which clinically was that of exudative erythema multiforme. After the multiform erythema had partially subsided the patient was treated with six injections of silver salvarsan. Thereupon a very severe and typical salvarsan examthem appeared. The question is raised by the author as to how such a patient should be treated for syphilis. The Wassermann reaction under this treatment had fortunately become negative. The author is of the opinion that the patient probably at a later date would tolerate small doses of neosalvarsan.

MERCURIAL AND OTHER METHODS OF TREATMENT.

Intravenous Injection of Cyanide of Mercury. Intravenous injection of cyanide of mercury was first advocated by Abadie in 1890. Milian¹ gives an interesting account of his experiences with the intravenous use of this drug. Milian uses 0.5 per cent. solution of cyanide of mercury in normal saline. The solution is then put in ampoules which should be sterilized. Daily injections of 2 c.c. are given and about 30 injections in all should be administered. Intravenous injection of this solution is painless and is without any action whatsoever on the blood-vessels or on the red blood corpuscles. A severe shock may result from too rapid injection of this solution. At least two minutes should be allowed to elapse from the beginning of the injection to the end. The tolerance of the patient to the average injection given according to this manner is very good. In some cases a mild stomatitis and in some cases a mild enteritis may result, but with care of the teeth and proper precautions, the patient will undergo the thirty injections without any disagreeable effect whatsoever. Immediately after injecting the drug the patient will experience the sensation of a metallic taste in the mouth in the same way as after

(9) *Dermat. Zeitschr.*, September, 1920.

(1) *Ann. des mal. vén.*, February, 1920.

arsphenamine injection the patient will have the sensation of smelling and tasting ether.

One feature of the cyanide is the effect it exercises upon the kidneys. Instead of there being an intolerance of the kidneys for this drug, it has, particularly in syphilitic albuminuria, a remarkably efficient action. Immediately after giving the injection there is a polyuria which continues for some time after the injection. Eventually the polyuria decreases, and may at the end of the series of injections, disappear. Syphilitic lesions of the kidneys, as manifested by the typical syphilitic albuminuria, yield very quickly to the cyanide of mercury intravenously.

Intravenous Injections of Iodized Oil. Through extensive experiments with horses and dogs, Cartier² came to the conclusion that iodized oil given intravenously was of great value and should be adopted in the treatment of various disorders in man.

It was found that *in vitro*, the iodine was disassociated only relatively slowly. The elimination, however, was quite rapid and towards the end of twenty-four hours no trace could be found in the blood. Careful autopsies were made of the animals to determine whether there was any tendency towards pulmonary embolism and this was found to exist in a very few cases and then only very small emboli had been formed.

After the experiments carried out by Cartier, Rathery treated five patients with 40 per cent. iodized oil at from four to six days intervals. The patients received five injections in all. The indications for these of the intravenous injection of iodized oil in the opinion of the author are chiefly cutaneous mycoses and late ulcerating gummatous syphilides.

The advantages claimed for this mode of administration of iodized oil are the following:

First, immediate absorption occurs obviating the slowness and uncertainty of the absorption which is the case when it is given subcutaneously.

Second, a fairly rapid decomposition takes place which results in an energetic action without, at the same time being accompanied by a toxic action.

(2) Bull. soc. franc. de dermat. et de syph., 1920, No. 7, p. 271.

Third, an exact dosage of the medicament is given.

In the discussion which followed the presentation of this paper, Simon stated that he had been using the intravenous injection of iodized oil since 1917 and had found the therapeutic results excellent and the tolerance perfect.

Lafay also gave his experience with the use of the iodized oil intravenously. He compares the administration of iodide in general with the iodized oil. In his opinion, the disadvantages of the iodides in general are the following:

The tolerance is markedly variable, and sometimes does not exist at all, regardless of what the mode of administration may be.

The passage through the body is very rapid and sometimes the injected iodide acts as merely a saline. Moreover there is a lack of localization of any permanency in the tissue.

There is a complete lack of penetration of the red blood cell and the elimination is very marked and very rapid.

The drug is congestive and sometimes hemorrhagic in its action and in some conditions it may provoke a veritable eosinophilia.

Moreover it is not only necessary to continue to give a large dose, but one must continue to increase the dose; otherwise, the therapeutic action greatly decreases with the increased tolerance of the patient.

The action of the iodized oil on the other hand, is exactly the opposite of that of iodides in general. It can be stated to be exactly the counterpart of all the disadvantages claimed for iodide in the foregoing paragraph.

Comparative Dissociation of Heavy and Light Calomel. The occasional failure of calomel in the prophylactic applications of the 33.33 per cent. calomel ointment led Duret in 1918 to make an attempt to get calomel which would be more rapidly dissociated than the ordinary sublimated calomel. Duret prepared his calomel by precipitation of the sublimated calomel. In this way he was able to get a product that occupied

three times the volume of the ordinary sublimated calomel and moreover was of much greater purity.

Gambier⁴ in carrying on the researches of Duret, has been able in the same way to produce a calomel which is five times lighter than the ordinary sublimated calomel. Dissociation experiments demonstrated the fact that this precipitated calomel produced by Gambier is seven and a half times more dissociable than the ordinary sublimated calomel which means that the activity of the calomel after dissociation is tremendously increased. So far as the author is aware there has been no failure in prophylaxis during a period of several years with the use of this precipitated calomel in the ointment used in the prophylactic application.

Treatment of Syphilis by the Query Serum. The remarkable results reported from France in the treatment of syphilis by Query serum led Sequeira⁵ to make a test of the treatment in his clinic. The serum is prepared by inoculating monkeys with a filtered culture of the organism which has been grown in bouillon. When the serum of the monkeys gives a strong positive Wassermann the animals are bled and the serum is collected and preserved in ampoules.

The first patient treated was a woman, 69 years old, who had gummatous ulcers on the leg and deafness. The patient had received about eleven injections of arsenical preparations in the course of two years without any improvement. After giving twenty injections subcutaneously of the Query serum, the ulcer was practically healed and the deafness had practically disappeared.

The second patient was a man 47 years of age with *tabes dorsalis* and with pronounced ataxic symptoms. He had had nothing but mercury and potassium iodide without any arsenical injections. After receiving twenty hypodermic injections of Query's serum, his pain disappeared and he was able to walk up and down the ward with his eyes closed.

The third patient treated was a woman 52 years of age with *tabes dorsalis* and severe lightning pains. She

(4) *Ann. des mal. vén.* January, 1920.

(5) *Lancet*, April 24, 1920.

had had mercurial and iodide treatment and nine injections of arsphenamine without any improvement; in fact she was steadily growing worse. After receiving seven injections of Query's serum, the frequency and severity of the pains had markedly diminished so that she was able to get through the whole day without resorting to pyramidon. Her general condition had also improved.

[Injection of foreign protein, particularly serum, has been found to be of considerable value in promoting the healing of even non-specific ulcers. The British syphilographers are loud in their denunciation of intraspinal treatment. In the opinion of the editor, one intraspinal treatment would have accomplished in either case of *tabes dorsalis* all that the twenty injections of monkey serum are said to have accomplished.—M.]

Röntgen-Ray Study of Absorption of Mercury. The intramuscular injection of mercury is a valuable method of administering this drug but there are certain disadvantages, chief among which is the uncertain absorption of the mercury. Especially is this true of the insoluble preparations.

Cole, Littman and Sollmann⁷ have studied the rate of absorption by means of the Röntgen ray. The absorption of insoluble mercury preparations can be followed admirably in this way. The method is not applicable to soluble preparations, however.

An intensive study of clinical cases gave the following as the time when absorption is completed:

Mercuric salicylate: By gluteal muscles, mean, 4 days; extremes, 4 to 10 days. By lumbar muscles, mean, 8½ days; extremes, 2 to beyond 24 days.

Calomel: Mean, 15 days; extremes, 4 to 39 days.

Gray oil: Unabsorbed during entire period of observation, a mean of 43 days; extremes of 16 to 125 days.

These findings indicate that gray oil injections are both inefficient and dangerous, and their use should be abandoned.

Calomel injections are also dangerous.

Mercuric salicylate injections, especially into the glu-

(7) Jour. Amer. Med. Ass'n., Dec. 4, 1920.

teal muscles, give a satisfactory absorption and present relatively little danger.

The authors have recently seen a case of poisoning from gray oil injections in which none of the drug had been received for four months. Roentgen-ray examination revealed large masses of metallic mercury globules.

Intramuscular Injections of Extract of the Posterior Lobe of the Hypophysis for Headaches. Since 1910 Bouveyron has been using the extracts of the posterior lobe of the hypophysis injected intramuscularly for syphilitic headaches, particularly that type which comes on late in the afternoon. As a rule, within five minutes after the injection, the headache disappears and does not reappear until the following day at the usual hour. It was found that the injection was of great value also in headache following the intravenous injection of arsphenamine. Likewise it is of value in the nitritoid crises. The injections are of considerable value in other types of headaches, particularly in the toxic febril headache, in which it acted not only in reducing the headache but in reducing the temperature as well.

Abortive Treatment of Syphilis. [The question of the possibility of aborting a syphilitic infection had given rise to much discussion. The consensus appears to be at the present time that if the treatment is begun before the Wassermann reaction has become positive, the possibilities of abortive treatment are very good. Sabouraud particularly has recently enunciated this opinion and has emphasized the importance of that observation.

In 1918 Lévy-Bing and Gerbay published some articles in which they showed that the Wassermann reaction becomes positive approximately the thirty-eighth day after the date of the infecting coitus. In other words, the date of the development of the chancre is of no consequence. The important period of time is that which elapses between the date of infection and the thirty-eighth day.—M.]

The same authors⁸ again emphasize the importance of this observation in the abortive treatment of syphilis. They maintain that in every recent case of syphilis there is a critical period in which the reaction

(8) *Ann. des mal. vén.*, August, 1920.

passes from the negative to the positive regardless of whether any treatment has been given or not. If the treatment is begun after this critical period, it does not prevent the Wassermann from becoming positive; whereas, on the other hand, if it is begun before this critical period has elapsed, the reaction does not become positive or if it does become positive only slightly so.

ARSPHENAMINE REACTIONS.

Serious Reactions from Diarsenol and Salvarsan. Four cases are reported by Moore and Foley¹ which show a type of reaction clinically familiar enough in its main points, but associated with unusual changes in the blood, which have heretofore not been generally known. In one of the cases which came to necropsy, pathologic evidence was offered which, partially at least, explains the blood picture; and in addition the fatal case revealed a kidney lesion which has been shown experimentally to be associated with intoxication with arsenical compounds, but which, so far as can be determined, has not been previously reported in human beings.

The essential characteristics of the blood picture are: Leukopenia, and absolute and relative decrease in the polymorphonuclear neutrophil cells, partially compensated for by a corresponding increase in the eosinophil and basophil granular cells and the large lymphocyte-transitional group; or, in a more severe grade of reaction, a practical disappearance from the blood stream of all granular cells, with the increase in the large lymphocyte-transitional groups more marked; while, if the reaction is maximally severe, all the leukocytic elements of the bone marrow are replaced by fragile forms, impossible of identification. The small lymphocyte cells, which owe their origin not to the bone marrow, but to the lymphoid elements of the body, are very little disturbed. Also there is generally evidence of disturbance of erythropoiesis and platelet formation.

Clinically, this leads to the suspicion that salvarsan and its allied products have a markedly toxic effect on the bone marrow; and this is borne out by the pathologic

(1) *Archiv. Dermat. and Syph.*, January, 1920.

findings—degenerative changes in the marrow with practical absence of mature leukocytic forms. This effect on the marrow is undoubtedly, when severe enough, the cause of death, first, by the production of a hemorrhagic diathesis (which led in one case to hemorrhages in the skin, lungs, bladder mucosa, suprarenals and kidneys); and second, by the failure of the body to react to the invasion of bacteria by the ordinary defensive mechanism, as seen in the non-cellular exudate in the lungs in spite of the presence of large numbers of bacteria.

Furthermore, the action of salvarsan on the bone marrow is apparently both toxic and stimulating; and, as was first surmised by Evans, this action is largely selective, depending in its selection on the extent of the damage done, until the poison, whatever its nature, overwhelms the whole bone marrow. The toxic action is apparent first on the neutrophilic granular cells, next on the eosinophilic and basophilic granular cells, and last of all on the large lymphocyte-transitional group; while the stimulating action is seen first in the eosinophils and basophils, and later, when they are decreased by toxicity, on the large lymphocyte-transitional group.

As stated above, the general clinical characteristics of these cases are fairly well known. Dermatitis, peripheral neuritis and nephritis are not uncommon events in arsenical poisoning. The interesting clinical feature is the blood picture, and it is to be hoped that careful observations will be made of similar cases.

The authors do not feel that the unusual blood findings in these cases can be ascribed to the accompanying dermatitis, though it is well known that in many skin diseases, among which is included exfoliative dermatitis from any cause, eosinophilia may be present. However, here the blood changes involve not only eosinophilia, but the whole bone marrow function, and in varying degree. This is sufficient to rule out the question of skin irritation. Furthermore, it is significant that one patient did not have a dermatitis; and other observations made at this clinic, as yet too incomplete to publish, indicate that the blood picture described here is by no means uncommon, and that it occurs in cases

which do not present the clinical reactive syndrome of arsenical dermatitis. On the other hand, a few cases of dermatitis have been followed with this point in mind, and have been found to be minus the blood picture. A more complete report will be made later on this point.

No explanation for the blood reaction is at present available. The most satisfactory theory is that there is some impurity in the drug, or some compound which produces the reaction.

Individual idiosyncrasy is always an unsatisfactory explanation, to be conjured up only as a last resort. Nevertheless, it is a well-known fact that if a patient develops dermatitis of the exfoliative type following arsenical therapy, he will in all probability have a similar reaction following any subsequent attempt to renew the salvarsan treatment.

There is a certain superficial analogy between the blood pictures and the microscopic picture of the bone marrow with those of benzol poisoning and anaphylactic shock. Salvarsan, of course, contains a double benzol ring, but no evidence can be found to show that in the body it breaks down into benzol. Investigation of its known products of decomposition along the lines of their selective toxicity for the bone marrow would be well worth while.

Another interesting point, in view of the necropsy findings in one case, is the kidney lesion. Three of the cases show no notable urinary findings, with the exception of evidence of kidney irritation—slight albuminuria and cylinduria. In one case the clinical findings with reference to the kidneys are much more striking—a definite early kidney irritation as evidenced by polyuria and inability to concentrate solids, a gradually decreasing phthalein output, and, two days before death, sudden and almost complete anuria with an outpouring of huge amounts of necrotic kidney substance, so much in fact that half the volume of the urine was taken up with this material. Following this, previously normal blood-urea nitrogen and non-protein nitrogen figures rapidly rose to the point usually associated with uremia.

So far as they were able to determine after a careful

examination of the available literature, the fatal case presents for the first time in the human subject the kidney lesion produced by Pearce and Brown in experimental animals (dogs) by the use of arsenicals. These workers were able to distinguish differences in the lesions produced by the several different preparations used (arsenious acid, atoxyl, arseticene, salvarsan, arsenophenyl-glycin). The lesions in this case seem to exhibit the character of both their salvarsan and arsenophenylglycin kidneys.

Generalized Arsenical Erythroderma (Sulfarsenol). Considerable interest has been manifested on the part of some men in sulfarsenol because of its reputed lack of toxicity. It is well known, however, that it is capable of inducing all of the reactions which arsphenamine or neo-arsphenamine may bring about and even arsenical generalized erythroderma. Hudelo and Rabut² report the case of a woman, 30 years of age, who had been given a series of intravenous sulfarsenol injections. After the eighth injection the patient developed a light urticarial attack, and after the tenth injection she developed a marked erythroderma. This was followed by a high temperature. The patient developed a very severe reaction indicating grave intoxication. The temperature remained high and vomiting and intense diarrhea followed. There was no albumin in the urine. Two hundred cubic centimeters of blood were drawn after which the patient was somewhat improved. At the suggestion of Ravaut, the patient was given sodium hyposulphite but although the woman was on the mend when the sodium hyposulphite was given, there was immediately a recurrence after which the sodium hyposulphite was withdrawn and the patient again commenced to improve. Despite ten injections of sulfarsenol, the patient suffered a recurrence of her vulvar syphilitic lesions and then it was decided to institute mercurial treatments; she was given mercurial injections and made an uneventful recovery.

Infection in Arsenical Erythema Scarlatiniforme. A case of scarlatiniform erythema developing during a course of arsphenamine therapy and having some un-

(2) Bull. soc. franc. de dermat. et de syph., 1920, p. 161.

usual pustules develop as a primary lesion is reported by Milian.³ After the second injection, numerous herpes simplex developed on the lip and after the third injection, a typical erythema of the scarlatiniform type appeared. After the fifth injection which was given thirty-three days after the beginning of the treatment, the same erythema appeared accompanied by numerous pustules as well as small pustulets, which when examined immediately after their formation were found to contain a staphylococcus.

Instead of decreasing the arsphenamine therapy, Milian increased the dosage from 0.45 to 0.75 grams after which the attacks of erythema ceased to appear. In the opinion of Milian the important feature of this case is that the pustules appeared simultaneously with the erythema and not consecutive to the erythema. In his opinion the arsphenamine acted as an awakener of the microbic infection in the same way that mercury gives rise to a stomatitis by increasing the virulence of the associated fusospirillum organism. To fit this phenomenon, Milian has coined the phrase of "arsenical staphylococcus biotropism."

Urticaria Consecutive to Injections of Neo-Arsphenamine. Another case of urticaria due to injections of neo-arsphenamine is reported by Bartet.⁴ The patient had never been attacked before by urticaria at any time during his life. The attacks of urticaria followed directly the intravenous injections of neo-arsphenamine and the severity of the attacks were in direct ratio to the size of the dose. Various attempts were made to eliminate or to obviate the urticaria without success. At last it was decided that the five day interval engendered the least amount of urticaria. After a search of the literature the author was unable to find in any place mention of urticaria following neo-arsphenamine.

Arsphenamine Icterus. Icterus developing during or following treatment by arsphenamine has been the subject of numerous articles but as yet no one has elucidated the pathogenicity. Brodier⁵ gives the results of his observations during the treatment of 636 syphilitics

(3) *Ann. des mal. vén.*, September, 1920.

(4) *Ann. de dermat. et de syph.*, 1919, p. 471.

(5) *Ann. des mal. vén.*, August, 1920.

by neo-arsenobenzol, (Billon), injected intravenously in daily doses which did not in any case exceed 0.6 at one injection. The total amount of arsphenamine injected in the different patients varied from 3.5 grams to 5.2 grams. Among the 636 syphilitics thus treated, there were thirty-nine cases of icterus or a percentage of 6.77.

There are two types of icterus which occurred in this series of cases. The first type which was by far the smaller in number developed during the course of the arsenical treatment. This type is spoken of as the "precocious icterus." The other type occurs at a later date. A number of syphilographers, among whom may be mentioned Milian, maintain that the precocious type of icterus is syphilitic in nature and is, so to speak, a recurrence whereas the late type of icterus is due to an intoxication by the arsphenamine. Other syphilographers maintain that either type may be looked upon as a catarrhal jaundice and may be induced directly or indirectly by the arsphenamine. Of the thirty-eight cases of icterus studied, eleven were of the early and twenty-seven of the late type.

Of the eleven cases of early icterus, ten of the cases were in the early secondary period of the infection. In five of these the chancre had been present for from only two to five months and of the other five it had occurred within three years. The amount of arsphenamine injected prior to the onset of icterus varied from 0.3 gram to 2.7 grams. No case resulted from the first injection of which the dose was invariably 0.15 gm. No relationship could be traced between the development of icterus and the series of numerals on the various specimens of arsphenamine. Alcoholism evidently played no part—at least no prominent part—in the development of the icterus.

Eight of the eleven cases of precocious icterus were treated for a period ranging from six weeks to two months with the injections of arsphenamine and in no case were there any untoward results.

Practically all of the precocious icterus cases developed the day following the injection. In two of the cases only it occurred the sixth and seventh days respectively after the injection. In the two cases the

icterus was preceded by ordinary signs of gastro-intestinal disturbance on the day following the injection and in one of these two cases, marked signs of intolerance developed the day following the injection consisting of fever and vomiting and gastro-intestinal disturbance. The patient had a marked intolerance for even very small doses.

All of the precocious cases of icterus recovered in a period varying from three weeks to one month. In nine of the cases there was no further antisyphilitic treatment during the period of the jaundice. In one case treatment was continued by intravenous injections of cyanide of mercury.

The late type of icterus is much more common than the early type. There were twenty-seven cases of this type. It most commonly developed in the first year of the infection and as a rule between the sixth and twelfth months. The total amount of neo-arsenobenzol injected before the onset of the late type of icterus varied from 3 grams to 5.5 grams. There is a direct relation existing between the total amount of arsphenamine injected and the percentage of the cases of icterus. The late cases seem to show a tendency to develop in series, differing in that respect from the early cases.

The date of the onset of the icterus in the late type varies from six days to three months and a half. The largest number of cases appeared about five weeks after the cessation of the treatment. There appeared to be no direct relation existing between the total amount of arsphenamine injected and the speed with which the jaundice appears.

Neither alcoholism, pregnancy, nor pulmonary tuberculosis seem to have any particular influence on the development of the icterus. Approximately half of the late type of icterus cases were subsequently treated with arsphenamine without any untoward results.

The authors conclude from their studies that icterus may be, in certain cases, an hepatic recurrence but that it does not seem to be directly the result of syphilis. They believe that arsphenamine in sufficient dosage favors indirectly the production of a toxic infectious icterus which is ordinarily benign in the patient pre-

disposed towards jaundice. Secondary syphilis, particularly from the sixth to the twelfth months, often produces a parenchymatous hepatitis the modifications of which are the principal causes predisposing to this type of icterus.

They advise caution in regard to treating patients with arsphenamine during the period of the icterus for the reason that it is possible that a benign icterus may be transformed thereby into a malignant icterus.

Icterus and Arsphenamine. Another group of 55 cases of icterus observed in the course of one year which had developed during the treatment of 1,100 cases of syphilis was reported by Clement-Simon and Vulliemoz.⁶ All the patients were ambulatory dispensary cases and therefore some of the studies which would otherwise have been carried out, were not made because of the inaccessibility of the patient.

The date of the appearance of the icterus varied within wide limits. In only one case did the icterus appear after a nitritoid crisis. In thirty-two cases the icterus was observed within one month after the last injection and quite frequently it appeared during the course of the series. In a number of cases, the patient who had received one series of injections without the development of icterus developed icterus during the course of the second series. In twenty-two cases, icterus developed more than one month after the last injection. In one case the icterus developed thirteen months after the end of the medication. No relationship seemed to exist between the duration of the syphilitic infection and the development of icterus. The symptoms of the icterus appeared to be about the same in all cases, namely, a retention icterus with marked coloration of the skin and the urine, and a decoloration of the feces. There were seventeen cases of non-dissociated icterus; that is to say, accompanied by the presence in the urine at the same time of bile pigment and biliary salt. In five cases of dissociated icterus there was an absence of the biliary salts found in the urine. Bradycardia and pruritus were symptoms observed in only a very few cases, and not even those which showed retention of the bile salts.

(6) Bull. soc. franc. de dermat. et de syph., July, 1920.

The Wassermann reaction was done only in a few cases during the course of the icterus. It was observed to be positive in four cases; in one case slightly positive, and twice it was found to be negative. No sign of active syphilis existed in forty-six of the fifty-five cases. The treatment had been instituted merely because of a positive reaction or, when the Wassermann was negative, because of an insufficient previous treatment. In nine of the cases there were clinical symptoms of syphilis. Four patients had been treated for secondary manifestations in evolution; one for a syphilitic chancre, and it was during the course of the series that the secondary manifestations appeared and the icterus had made its appearance. In three cases the co-existence of secondary symptoms and icterus, a co-existence which was first described by Fournier, was observed. All three cases had previously been treated for secondary symptoms and it was during the period of repose that the icterus and the further secondary manifestations made their appearance.

The duration of the icterus varied between three and five weeks. In all the cases it spontaneously disappeared. Most of the patients continued their occupations and did not even go on the milk and vegetable diet which was prescribed for them. The treatment was very simple and consisted of a calomel purgation. No arsenical treatment was given those patients who had had no active manifestations but patients who did present active manifestations were given further arsenical medication during the attack of icterus and these individuals made, likewise, uneventful recoveries.

The prognosis of arsphenamine icterus is excellent. Not one of the patients had any untoward permanent result following the attack of icterus. No *icterus gravis* developed and no sign of sclerosis of the liver appeared. There appeared to be little if any relation existing between signs of intolerance and the development of icterus. Only in eleven cases had there been previous reaction such as headaches, vomiting and fatigue. All of these cases appeared in dispensary practice and the authors state that in their extensive private practice only

one case of icterus had been observed. No attempt is made by the authors to explain the cause of the icterus.

In a group of twenty-four cases in the hospital at Fez, Nicaud⁴ observed eight cases of early icterus and sixteen cases of late icterus due to arsphenamine injections.

In his opinion, the real cause of these icterus cases is, without doubt, the arsenic injected. The dead bacteria contained in the distilled water, the traces of lead, the rapidity of the injections and the concentration of the arsphenamine are merely secondary factors. Pre-existing lymphatic lesions may serve to localize the lesions in the liver. The author states that neo-arsphenamine has only a slightly hemolytic action *in vivo* and that arsphenamine, on the contrary, has no hemolytic action either *in vivo* or *in vitro*. [This statement is exactly the opposite of the experimental work carried out by Schamberg and his coworkers.—M.]

In the late cases, the author contends that the icterus is due to an accumulation of arsenic and of insufficient renal elimination. He believes that the renal elimination is the index of the retention of arsenic and that when the elimination becomes lowered, one should be on guard against the possible occurrence of the retention of arsenic and, therefore, the occurrence of icterus.

Polyneuritis Following Neo-Arsphenamine. The association of polyneuritis and dermatitis exfoliativa following intravenous use of the arsenical preparations was first mentioned by Duhot in 1912. Beeson⁵ has recently observed and studied a patient who developed polyneuritis and dermatitis exfoliativa after a series of neo-arsphenamine injections. Inasmuch as dermatitis exfoliativa is relatively common and polyneuritis relatively rare, after intravenous injections of the arsenical preparations, Beeson confines his discussion largely to the polyneuritic syndrome in his case.

As a rule the onset of polyneuritis is marked by formication and pain in the soles and calves. The feet and legs become edematous, the skin reddened and a fur-

(4) *Presse méd.*, May 22, 1920.

(5) *Archiv. Dermat. and Syph.*, September, 1920.

furaceous scaling appears. When the trouble is of more serious nature the successive disappearance of the plan-tar, Achilles and patellar reflexes is noted; cramps in the calves associated with the loss of muscular power in the legs and even paralysis. Similar but less marked symptoms appear in the hands and arms. As a rule there is no evidence of rectal or vesical disturbance.

The patient who was seen by Beeson was a negro, 42 years of age, admitted to hospital in March, 1919. He had no active manifestation of syphilis, other than a postive Wassermann. Antisyphilitic treatment was begun and carried out as follows: The first course consisted of six weekly intravenous injections of neo-arsphenamine (neodiarsenol brand) given in concentrated solution. The initial dose was 0.6 grams and later 0.9 grams. In addition to the injections of arsphenamine he was given about twelve intramuscular injections of mercuric chloride. No evidence of intolerance appeared during this time. After a three weeks' rest, a second course was begun, inasmuch as the patient's Wassermann reaction was still positive. He had received two more weekly injections of neo-arsphenamine of 0.9 gms. each when he suddenly became ill and was admitted to the hospital the day following his last treatment. The cutaneous eruption at first was urticarial in type which later became a generalized exfoliative dermatitis. About two months after admission the patient exhibited a slight steppage gait. His hands also began to show signs of weakness and it was difficult for him to grasp and retain objects. A little later a foot and wrist drop appeared. Beginning in the toes and fingers, this condition gradually extended upward to the lower part of the legs and to the forearms, although they were affected to a lesser degree than the more distal parts. By this time he could not stand or raise himself up and had to be fed. The Achilles reflexes were almost abolished, but the knee-jerks showed only a slight diminution. The affected muscles were tender on pressure. Muscular atrophy appeared soon after the paralysis, coming first in the feet and hands and thence extending centripetally in a like manner. There was no interference with either the rectum or bladder control.

In the course of about four months the patient made complete recovery. The steppage gait was the last symptom to disappear.

Beeson believes that syphilis can be excluded as an etiologic factor in the case inasmuch as cases of multiple neuritis due to that disease are, as a rule, observed during the secondary period in association with active skin manifestations. The fact that the author's patient recovered without further specific treatment would also appear to be an argument against syphilis. Both syphilis and alcohol, however, were possibly contributory causes.

Asthma Induced by Neo-Arsphenamine. A case of asthma induced by neo-arsphenamine is reported by Mouradian.⁶ The patient was a female, 38 years of age, who had been a luetic for fifteen years and had received continuous treatment, and in whom the Wassermann reaction was positive. Until coming under the observation of the author no arsphenamine had been administered. At the time of beginning treatment there was a slight chronic bronchitis which had been present for several years. A series of gradually increasing doses of arsphenamine was given. When the dosage reached 0.75 the patient was seized with a nervous crisis which simulated hysteria. The next dose was reduced to 0.45 and was followed by fever and an attack of asthma which lasted four days. The next injection consisted of 0.6 and, probably because of the use of adrenalin, was not followed by a crisis, but a week later in spite of the use of adrenalin 0.6 of arsphenamine induced a severe attack. After two months the injections were resumed, with practically the same result, whereupon they were discontinued.

EXPERIMENTAL WORK ON ARSPHENAMINE REACTIONS.

Investigations Bearing on the Cause of Arsphenamine Reactions. Since the introduction of the organic arsenicals in the treatment of syphilis, great interest has been manifested in the study of the systemic reactions following the use of arsphenamine and neo-arsphenamine, as well as in the underlying causes of these reactions.

(6) Bull. de soc. franc. dermat. et de syph., June, 1920.

A considerable literature has grown up on this subject—much of it of a controversial character. While considerable light has already been shed, many practical and important phases of the problem are still obscure. The studies by Schamberg, Kolmer, Raiziss, and Weiss⁷ were undertaken with the view of aiding in the clarification of this complicated subject.

The literature concerning the earlier investigations need not be given in detail, as it has been reviewed by many writers. The more recent and meritorious studies of Danyasz are deserving of careful thought. In 1917 Danyasz published his ingenious "precipitation hypothesis" as an explanation of the causes of reactions following arsphenamine and neo-arsphenamine. He states:

"A short time after the injection of a disodium solution of arsenobenzol (arsphenamine) this compound loses the sodium which combines with the free carbonic acid forming sodium bicarbonate, leaving the arsenobenzol as an insoluble base. At the same time part of the arsenobenzol which remains as a monosodium or disodium salt combines with the calcium phosphates, also producing an insoluble compound. The presence in the blood of free oxygen and sodium chloride hastens these transformations, while the organic bases contained in the plasma form with the insoluble deposit new soluble compounds."

The ingenious theory advanced by Danyasz, however, is only in part true. It explains the well-known precipitation of solutions of acid arsphenamine and probably also concentrated solutions of monosodium arsphenamine (*i. e.*, arsphenamine neutralized to the point of clearing). There is no adequate evidence, however, that precipitation occurs after the use of disodium arsphenamine (hyperalkaline solutions), and there is no evidence at all that neo-arsphenamine is ever precipitated in the blood. The mechanism which Danyasz sets forth as the cause of the precipitation, namely, conversion of the sodium salt of the drug into the insoluble base through the interaction of the sodium salt with the carbonates, phosphates and other inorganic salts of the blood, is not supported by experimental evidence.

Experiments carried out by the authors indicate that

(7) Archiv. Dermat. and Syph., March, 1920.

the phosphates of calcium, magnesium, sodium and potassium in the concentrations in which they normally occur in the blood, do not precipitate alkaline solutions of arsphenamine and neo-arsphenamine *in vitro*, either when tested alone or in the presence of the other organic or inorganic constituents of the blood.

Sodium bicarbonate alone forms a faint flocculation with minute amounts of disodium arsphenamine, but the precipitate dissolves readily on the addition of greater amounts of the latter. Acid arsphenamine precipitates readily in the presence of many of the inorganic salts of the blood; the precipitate, however, disappears when an excess of arsphenamine is added. Solutions containing even double the blood content of inorganic salts in an organic and protein menstruum ("artificial blood") do not form any appreciable precipitates with disodium arsphenamine *in vitro*. A faint flocculation which occurs occasionally with the first drop of arsphenamine, disappears when the second drop has been added. Neo-arsphenamine is not precipitated by any of the organic or inorganic salts of the blood. They believe that if arsphenamine is properly neutralized, that is, if the disodium and not the monosodium arsphenamine is injected, precipitation *in vitro* can scarcely take place.

Experiments on the precipitation of arsphenamine with human blood *in vitro* yielded the following results: (a) Acid solutions of arsphenamine in a concentration of 0.25 per cent. or more will precipitate in the presence of human serum *in vitro*. (b) Disodium-arsphenamine is not precipitated. (c) Monosodium arsphenamine is precipitated when added in very small quantities to human serum, the precipitate clearing on the addition of larger amounts, doubtless owing to the contained alkali. (d) When arsphenamine is dissolved in physiologic salt solution instead of distilled water, the results are not appreciably different. (e) Neo-arsphenamine even in 40 per cent. solution is not precipitated in the presence of human serum.

The fact that arsphenamine is hemolytic in practically all of the concentrations in which it is employed and that neo-arsphenamine is not hemolytic except in very dilute solutions (0.9 gm. in 180 c.c. of water) or in

extremely concentrated solutions (0.9 gm. in from 2 to 3 c.c.) shed a degree of illumination on the relative manner in which these drugs are clinically tolerated. Another fact of importance is the hydrogen-ion concentration of these two compounds. The hydrogen-ion concentration of neo-arsphenamine is 7.0 to 7.4 which is approximately that of the blood. That of acid arsphenamine is 4.7, while the alkaline solutions are beyond 9.

The injections of acid solutions of arsphenamine are prone to produce death, or if less concentrated, may lead to the development of a bronchopneumonia as a result of intravascular precipitation of the drug. Concentrated monosodium arsphenamine solutions may, under certain conditions, likewise cause death, or in the event of recovery cause an embolic bronchopneumonia. There is no evidence that pneumonia symptoms have ever developed after the use of disodium arsphenamine, nor after the use of neo-arsphenamine.

The injection of cloudy or turbid solutions of neo-arsphenamine will almost invariably give rise to severe nitritoid symptoms in which syncope and shock-like collapse are the outstanding features. No pulmonary symptoms follow. Neo-arsphenamine (and of course arsphenamine) should never be administered unless the solution is perfectly clear.

Nitritoid reactions may at times follow the injection of a clear solution of neo-arsphenamine. As neo-arsphenamine is never precipitated in the blood, the elucidation of the cause of such reactions must be sought elsewhere.

The studies lead to a reiteration of the view previously expressed that the nitritoid reactions are related to some inherent property of the drug. In no other manner could the variation in the incidence of reactions with different lots and different brands of the drug be explained. The cause is probably due to traces of an unidentified impurity which for purposes of convenience and easy reference the authors have designated "Substance X."

The Chemistry of Arsphenamine and Its Relation to Toxicity. Many attempts are being made to determine the cause of the toxicity of arsphenamine. The work of

Raiziss and Proskouriakoff⁸ is an attempt to solve the problem by a study of the chemistry of the drug. The analyses for arsenic nitrogen and other elements in most of the samples correspond to the formula having two molecules of water of crystallization. Ehrlich and Bertheim thought that the compound crystallized with one molecule of methyl alcohol. Kober called attention to the fact that there is no definite proof of the presence of two molecules of water in the crystallization. He was inclined to admit the presence of one molecule of methyl alcohol because arsphenamine usually is precipitated from solutions containing methyl alcohol. The comparatively rapid oxidation of arsphenamine when dissolved in water or organic solvents, the difficulty of obtaining it in crystalline form and other factors, make the purification of the drug practically impossible.

According to its chemical formula with either two molecules of water crystallization, or one molecule of methyl alcohol, arsphenamine contains 31.6 per cent. and 31.85 per cent. of arsenic respectively. A lower arsenic content would indicate moisture, methyl alcohol, ether or other organic solvents as the result of insufficient drying. Inorganic impurities, such as calcium or magnesium chloride or salts of heavy metals also lower the percentage of arsenic. Higher arsenic content, on the other hand, may result from a loss of water or methyl alcohol of crystallization by too vigorous drying, and also by the presence of other impurities, such as poly-arsenical compounds. The higher arsenic content may indicate the presence of arsenophenols or inorganic arsenical compounds.

According to the graphic formula, arsphenamine should contain 5.89 per cent. of nitrogen. The chemical analyses of the authors show that the percentage of nitrogen in normal as well as in toxic lots of arsphenamine is only the theoretical amount.

Quantitative estimation of either arsenic or nitrogen, or both, in arsphenamine does not give one a proper idea as to its purity in order to evaluate properly its chemical purity one should consider the ratio between the percentage of arsenic and that of nitrogen. The

(8) Archiv. Dermat. and Syph., 1920, p. 280.

theoretical percentage of arsenic in arsphenamine is 31.6, of nitrogen 5.89; the ratio of 5.37. Examination of various lots showed that there might be a slight variation in this ratio. This variation may arise from the presence of an impurity containing more arsenic and less nitrogen than arsphenamine, as, for example, tetramino-tetra hydrox-arsenobenzene-tetra-hydrochloride which contains 26.13 per cent. arsenic and 9.76 per cent. nitrogen. This is also more toxic than arsphenamine. The results obtained by the analysis of a mixture of 90 per cent. arsphenamine and 10 per cent. tratra-mino compound would give the above low ratio.

Thus it is seen that a valuable measure of the chemical purity of arsphenamine lies in the ratio of arsenic to nitrogen. Arsenic exists in arsphenamine in a trivalent state. In order to determine whether a certain compound is over or under reduced it is best to establish a relationship between the arsenic content and the oxygen value because the latter value is dependent entirely upon the arsenic radical and, hence, on the amount of arsenic. The theoretical arsenic-oxygen ratio is 2.34. The results of the analyses showed that the ratio differed but slightly from the theoretical value. The largest differences were only 4.3 per cent.

Compounds which did not pass the animal toxicity test or were found to cause reactions in patients had an approximately normal arsenic oxygen ratio. It is evident then that the cause of toxicity or reactions can not be attributed to the presence of arsenoxide or arsin.

The analytical study of arsphenamine leads one to believe that the impurity causing reactions in patients is present only in very small quantity.

Determination of the Toxicity of Arsphenamine. Inasmuch as arsenoxide is twenty times more toxic than arsphenamine it is very necessary that the amount of this toxic substance should be determined in the arsphenamine.

A method for the determination of arsenoxide first proposed by Ehrlich has been used by Cousin⁹ to determine the arsenoxide content in a series of arsphenamine preparations. The method is a simple one and can be carried out in any ordinarily equipped laboratory. The

(9) Bull. soc. franc. de dermat. et de syph., June, 1920.

method consists in dissolving 1 gram of arsphenamine in 10 c.c. of methyl alcohol. The drug should go into solution promptly if it is pure. The solution is then made up to 100 c.c. with distilled water. The solution should be perfectly clear and yellow; if there is any brownish coloration it means that oxidation has taken place and the drug is, therefore, impure. To this solution is then added 1.5 grams calcium carbonate. The calcium carbonate combines with the hydrochloric acid of the arsphenamine and the base which is thereby liberated, is precipitated completely because it is insoluble in water. The arsenoxide, on the contrary, remains in solution. The solution is then filtered and 50 c.c. of the liquid is diluted with 75 c.c. of distilled water. To this are added 5 c.c. of normal hydrochloric acid and a few drops of starch solution. The arsenoxide content is then titrated by means of a twentieth normal solution of iodine. When the end point of the titration is reached, a bright blue coloration of the fluid results because of the action of the iodine on the starch. This titration is calculated very readily inasmuch as the dilution of the solution is such that 1 c.c. of the iodine solution corresponds roughly to 1 per cent. arsenoxide content. According to Ehrlich, a good preparation of arsphenamine should not contain more than 0.5 per cent. arsenoxide.

The chemical analysis of a number of preparations of arsphenamine showed that those preparations having a high arsenoxide content gave the more severe reaction. Therefore, the author feels that the determination of the arsenoxide content is a direct method of determining the toxicity of the drug.

[The results of the work of Raiziss and Proskouriakoff (*vide supra*) would indicate that the arsenoxide content does not determine the toxicity of arsphenamine.—M.]

Toxicity of Arsphenamine and Neo-Arsphenamine. A description of the method and the results of the studies as carried out in the Hygienic Laboratory, U. S. Public Health Service, in testing the toxicity of arsphenamine, are given by George B. Roth.¹ In the official method for testing arsphenamine, it is required that

(1) Archiv. Dermat. and Syph., September, 1920.

white rats weighing from 100 to 150 grams shall tolerate 100 milligrams per kilogram of the drug for forty-eight hours when given intravenously as a 2 per cent. alkaline solution; 0.9 c.c. of normal sodium hydroxid being used for 100 milligrams of arsphenamine. White rats are re-

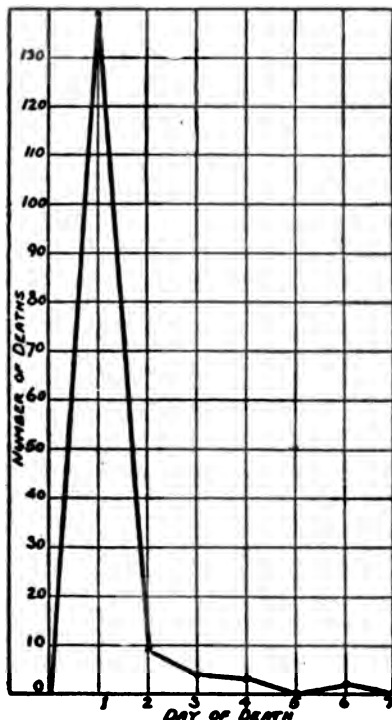


Fig. 17. Death rate and time of death of rats treated with arsphenamine.

quired to tolerate 200 milligrams per kilogram of neo-arsphenamine for seven days when given intravenously as a 4 per cent. aqueous solution. It is further required that for both compounds the rate of injection shall be twelve to fifteen seconds for every 0.1 c.c. of solution.

A statistical study of the death rate and time of death of the rats used in the official testing of arsphenamine

showed that a little over 80 per cent. of the animals that died within fourteen days did so within twenty-four hours, and that almost 90 per cent. of the deaths occurred within the first forty-eight hours. On the other hand, similar computations for neo-arsphenamine gave figures which contrasted markedly with those obtained for arsphenamine. Approximately 5 per cent. of the deaths from neo-arsphenamine occurred within the first day, 15 per cent. within the first two days, 30 per cent.

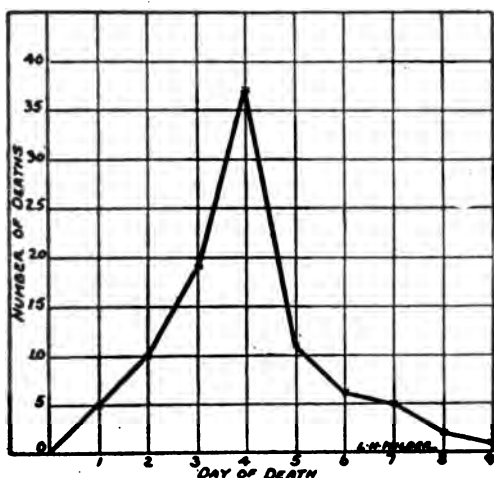


Fig. 18. Death rate and time of death of rats treated with neo-arsphenamine.

within the first three days and 60 per cent. within the first four days.

Experiments were carried out on white rats in which the official rate of administration was used, the results of which demonstrate that the toxicity of arsphenamine under certain conditions increases as the concentration increases. The increase in toxicity is strikingly demonstrated by the more toxic acid solutions of arsphenamine. The experiments indicate that the concentration and the rate of injection are very important factors in the determination of the toxicity of the drug (Fig. 17).

The relation of solubility of neo-arsphenamine to its toxicity was carefully studied. The results indicate that any preparation of neo-arsphenamine which does not go into solution readily should not be used because the process of shaking so oxidizes the drug that if it were not already toxic, it rapidly becomes so during the process of shaking (Fig. 18).

The comparison of the products of various manufacturers indicates that arsphenamine products made in the United States are generally less toxic than those of foreign manufacture, and that the neo-arsphenamine preparations made in this country compare favorably, and in certain instances are decidedly less toxic than those of foreign manufacture.

Hemolytic Activity of Solutions of Arsphenamine and Neo-Arsphenamine. The hemolytic activity of the solutions prepared in the usual way has been determined by Kolmer and Yagle² and the methods by which the hemolysis may be avoided are described.

All solutions of arsphenamine are found to be hemolytic, due to the direct hemolytic activity of the arsphenamine itself. This hemolysis may be avoided by using isotonic saline solution and when this is used the solution becomes from three to ten times less hemolytic than in solution in water. The addition of the alkali in neutralization increases the hemolytic activity. Concentrated solutions in water and isotonic saline are more hemolytic than dilute solutions. On the other hand, neo-arsphenamine is not hemolytic, except in dilute solutions in water. The full dose of 9/10 grams given in 30 c.c. or less of water is not at all hemolytic owing to the presence of sufficient inorganic salts from the drug to render the solution approximately isotonic.

The degree of hemolysis produced by arsphenamine may be lessened (1) by using saline solution instead of sterile water; (2) by avoiding the administration of concentrated solutions; (3) by carefully neutralizing and clearing the solution with sodium hydroxide and not adding an excess; (4) by giving the injections slowly so as to permit gradual mixing and dilution of the solution with the blood.

(2) Jour. Amer. Med. Ass'n., March 6, 1920.

Histopathologic Changes Produced by Arsphenamine and Neo-Arsphenamine. In determining the toxicity or organotropism of new compounds in the course of chemotherapeutic investigations, the general custom is to administer solutions to experimental animals and arrive at conclusions on the basis of dosage in relation to the duration of life. The purpose of the investigations of Kolmer and Lucke³ was to study the histopathologic changes produced in rats and rabbits by the intravenous injection of single large and multiple small doses of arsphenamine and neo-arsphenamine as bearing on the use of these compounds for the treatment of disease among persons and in relation to chemotherapeutic studies with new arsenical compounds prepared by Kolmer, Schamberg and Raiziss.

Necropsy examinations of animals was made at varying intervals after injection. The histopathologic changes have varied in degree among animals receiving the same compound under identical conditions and have generally been somewhat more severe among the rats than among the rabbits.

The tissue injuries produced by neo-arsphenamine have generally been of the same character as those produced by arsphenamine, but, in comparison to dosage, have been less severe. Acid or non-neutralized solutions of arsphenamine produced severe vascular injuries in all organs, characterized by congestion, hemorrhagic extravasations and the production of peculiar thrombi composed presumably of precipitates, conglutinated and hemolyzed erythrocytes. Secondary cellular degenerations and necroses followed.

Single large doses of arsphenamine and neo-arsphenamine also produced similar vascular changes of congestion, hemorrhage and thrombi of conglutinated erythrocytes in the various organs, but in a much milder degree; areas of focal necrosis and cellular degenerations in heart muscles, liver and spleen were rather prominent. The kidney lesions were composed of these vascular changes and varying degrees of tubular necrosis; the suprarenals showed well-marked changes in lipid and

(3) *Archiv. Dermat. and Syph.*, September, 1920.

chromaffin contents in addition to vascular changes and cellular degenerations.

Multiple small doses of arsphenamine and neo-arsphenamine produced slight vascular changes of congestion and thrombi of conglutinated erythrocytes in the various organs; focal areas of cellular degenerations and necroses were frequently well-marked, particularly in the heart and liver. The kidneys usually showed vascular and tubular changes, and the suprarenals various changes, including alterations in the lipid and chromaffin contents.

Tubing as a Cause of Reaction After Intravenous Injections. Several epidemics of sharp reactions following intravenous injections of arsphenamine led to the discovery by Stokes and Busman⁴ of the fact that the reactions were due to new pure gum rubber tubing used in giving the injection. It was found that there were two types of tubing, one of which when new would not give the reaction; the other when new, even after prolonged boiling and rinsing with water, would give very sharp reactions, characterized by chill, rise in temperature coming on from thirty minutes to an hour after the injection accompanied by nausea, vomiting, diarrhea, pain in the head and back, and varying degrees of prostration. Experimentally, it was found that the toxic substance gradually disappears from the tubing on use but that it could be apparently removed in a short time by soaking the tubing in normal sodium hydroxide solution and rinsing. A typical reaction was produced experimentally in dogs. The identity and toxicology of the poisonous principle are under investigation.

(4) Jour. Amer. Med. Ass'n., April 10, 1920.

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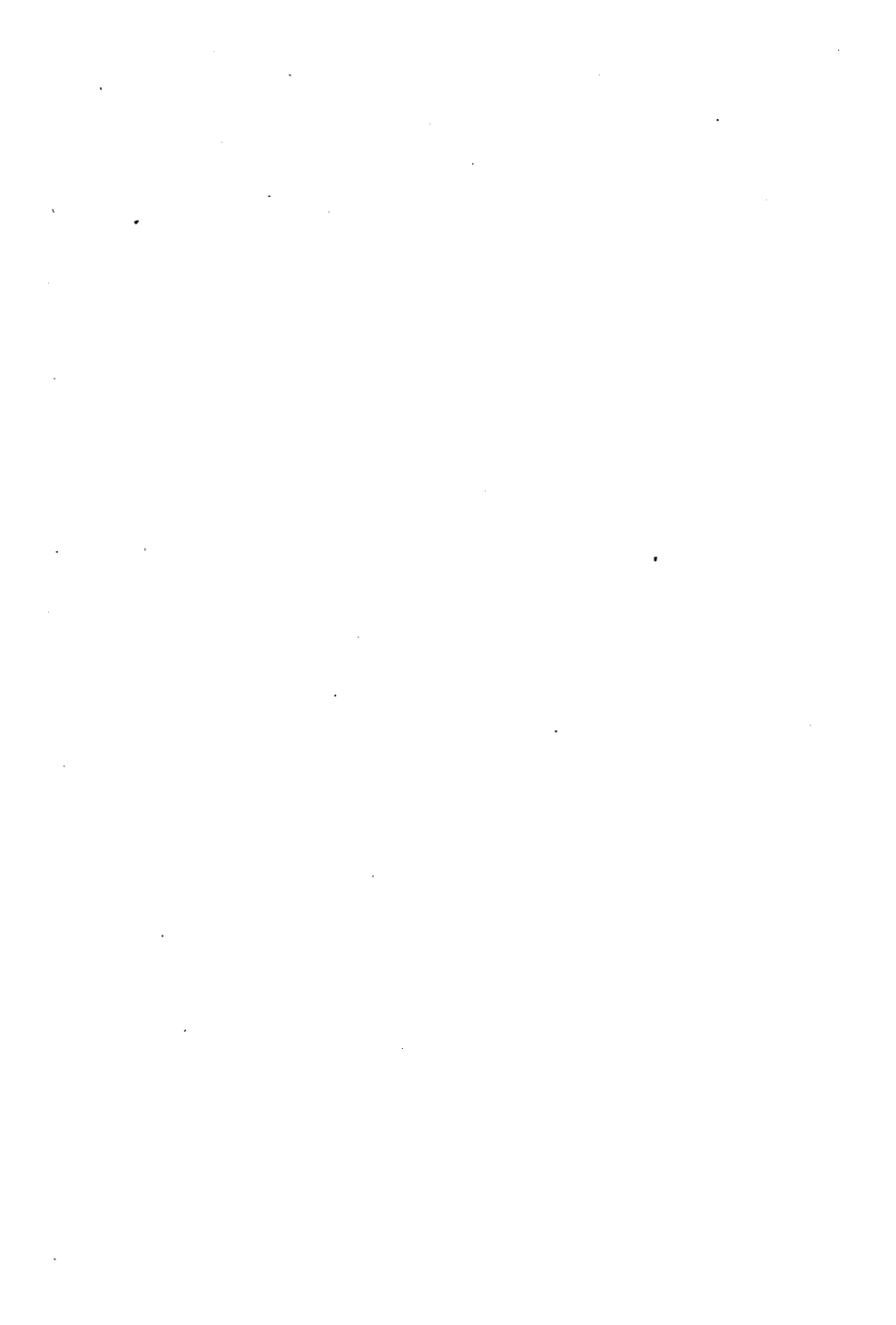
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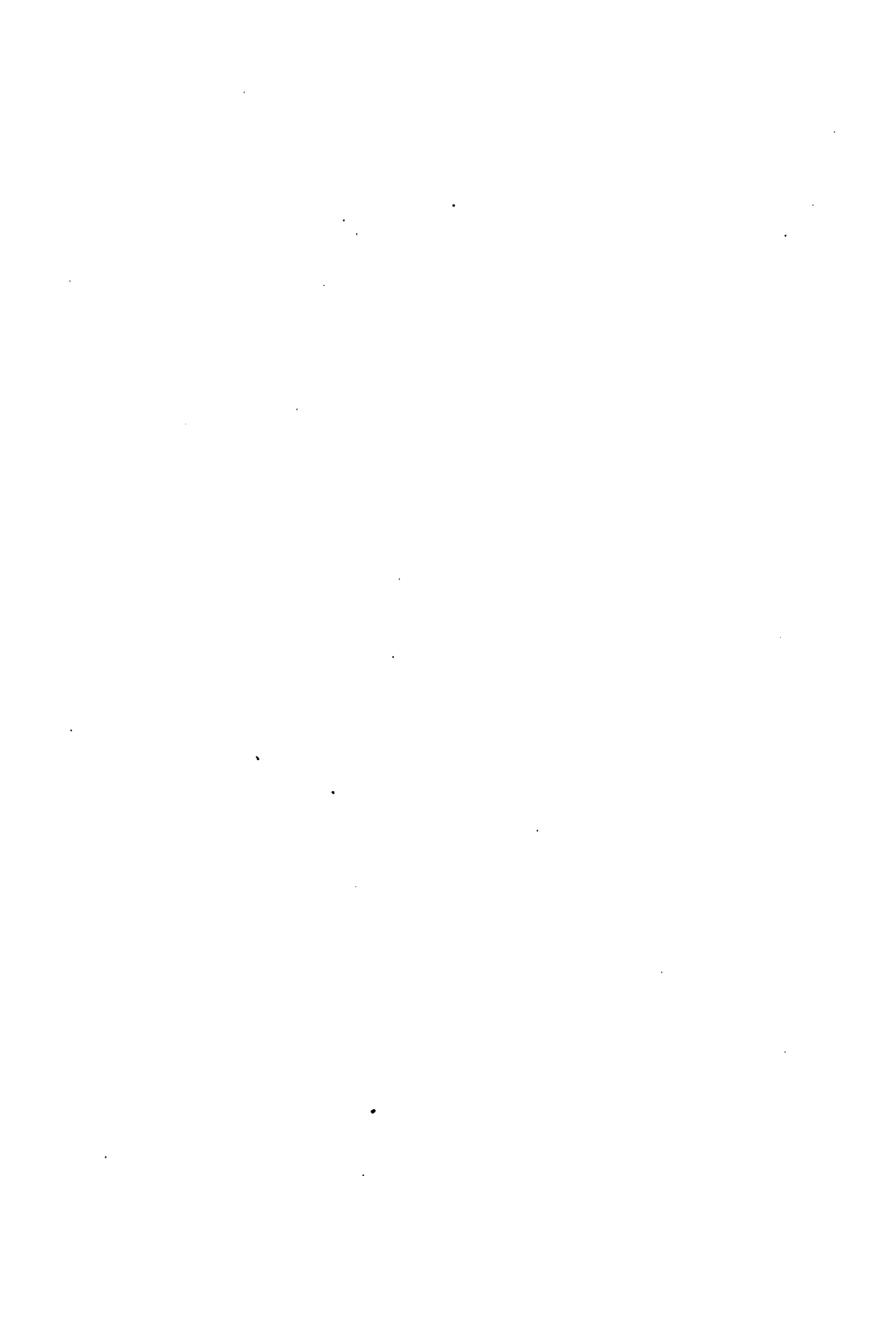
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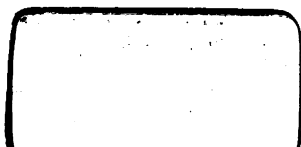
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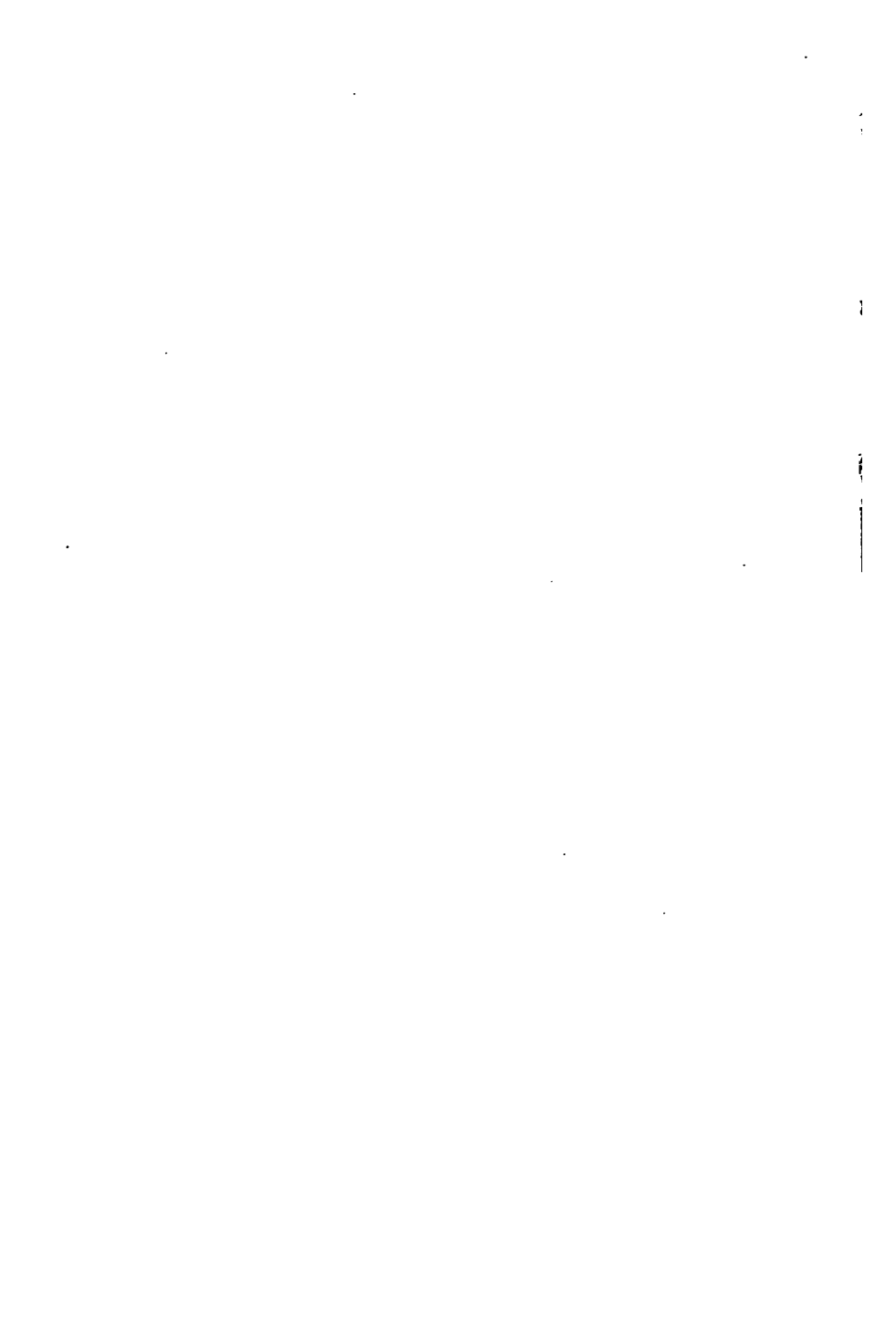




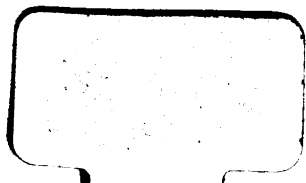


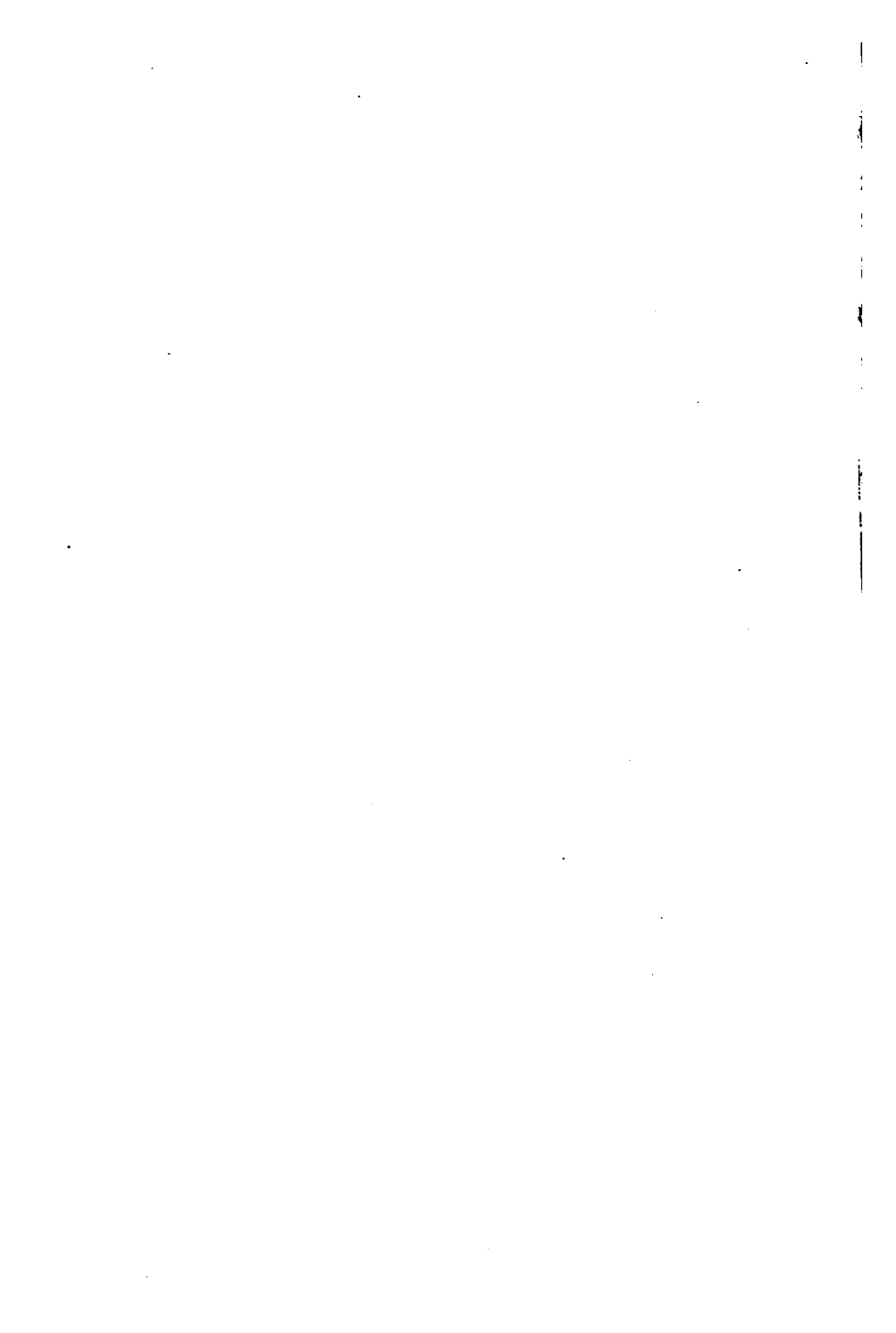
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